Spatial and contextual long-term and working memory in ageing and disease



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Abstract

Initially thought to be two independent memory systems, working memory (WM) and long-term memory (LTM) both present associative features controlled by the medial temporal lobe (MTL). Despite their similarities, the two memory systems have mostly been explored and compared using distinct methods and measures. Considering their differences and their correspondences, this thesis focuses on spatial associative WM and LTM performance in healthy ageing and in the presence of MTL impairment. The studies presented investigate the mechanisms of the two memory systems, their interplay, and the modulatory relationship between them and attention, using analogous tasks and equivalent behavioural measures. Specifically, Chapter 2 explores if retro-cueing benefits, previously observed in WM, extend to LTM retrieval, and whether this could represent a means of ameliorating age-related LTM impairment. Next, in Chapter 3, I compare the performance of young and older healthy adults in a spatial memory task on two devices – a personal computer and an immersive VR device – to test whether old adults benefit from an increased level of immersion and determine the optimal methods of measuring spatial memory. In the second study, I use a navigation-based memory task measuring WM and LTM, to investigate their patterns of use and interplay that might change with ageing. Lastly, Chapter 4 relies on the same task and aims to analyse patterns of performance modulated by different levels of MTL impairment in old healthy adults and individuals with limbic encephalitis. The results propose that WM and LTM show age-related associative deficits and that their interplay is preserved in ageing, despite old adults' increased forgetting. Additionally, they suggest that WM and LTM may rely on different retro-cueing mechanisms. Lastly, the most noteworthy outcomes are the tasks developed to measure spatial associative memory of different timespans in equivalent ways, using analogous steps and stimuli, which can become great tools in the research of WM and LTM retrieval processes.

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Statement of Contribution

This thesis reflects the collaborative nature of science. Therefore, it is important to note that the work presented was conducted with the support of colleagues both in and outside my supervisory team. The tasks used in Chapter 2 were designed in collaboration with Kia Nobre and Nahid Zokaei, building on previous work of Nora Rouast and Giedre Cepukaityte. Thomas Graham contributed to the collection of pilot data for the study, and I tested the rest of the participants and led the data analysis. The first study of Chapter 3 was built on the work of Alexander Von Klemperer, with guidance from Kia Nobre, Chris Butler and Nahid Zokaei. The second study was designed in collaboration with Kia Nobre, Nahid Zokaei and Dejan Draschkow. For both studies I led the data collection and analysis. Finally, I designed Chapter 4 together with Kia Nobre, Chris Butler and Georgios Argyropoulos and I ran the data collection and analysis. The writing in this doctoral thesis is my own, and was completed under the supervision of Kia Nobre, Nahid Zokaei and Chris Butler.

Impact of the COVID-19 pandemic

As so many things over the past two years, my research was negatively impacted by the ongoing COVID-19 pandemic. One of the studies presented in this thesis relied on behavioural testing of healthy elderly adults and individuals diagnosed with limbic encephalitis, all over 60 years old. Testing was achieved either at the John Radcliffe Hospital in Oxford, which required them to travel, or at their homes which involved me travelling there, also increasing their risk of infection. To collect a complete dataset, testing was scheduled for the spring of 2020. Given the circumstances, all appointments had to be cancelled and data collection could not resume before the completion of this thesis. Additionally, I was unable to implement a study that had been designed and piloted on time. This was aiming to explore the neural correlates of retro-cueing in LTM.

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1. General Introduction

Except for those occasional moments when memory fails to retrieve a particular fact on demand, or when someone we know suffers from memory loss, most of us are unaware that almost every one of our actions and interactions relies on the proper functioning of memory. In fact, so much do we depend on our memory that without it we would lose our ability to identify, adapt to and respond to our environments, to communicate, think critically and reminisce about past experiences.

For this reason, within the scientific arena, memory has received considerable attention and has been the protagonist of a vast, rapidly growing body of research since the 19th century. Over time, the breadth of concepts encompassed by the term "memory" has widened. When guided by time span, memory can be categorised into iconic memory, the brief lingering of sensory stimulation, working memory (WM), and long-term memory (LTM). This thesis will exclusively focus on WM and LTM retrieval.

Originally, Atkinson and Shiffrin (1968) defined short-term memory (STM) as individuals' ability to keep in mind limited amounts of information of any kind for short durations (Atkinson & Shiffrin, 1968). Short-term memory stores the outcome of the transformation of sensory stimulation into cognitive information after the stimulation is no longer present. However, when considering our ability to manipulate this stored information through executive functions, we refer to WM (Baddeley, 1983). In spite of the different theories, STM and WM are often used interchangeably (Aben, Stapert, & Blokland, 2012). The blurred distinction between the two constructs currently present in the literature is also mirrored in this thesis, where the term WM is used, although no explicit manipulation of information is required to perform the tasks successfully.

Separately, LTM represents individuals' ability to store great amounts of information for extended periods. According to Tulving's seminal theory, LTM is made up of semantic memory, our ability to remember atemporal facts and general knowledge about the world, and

episodic memory, meaning "temporally dated episodes or events, and the temporal-spatial relations" between them (Tulving, 1972, 2002). The latter holds information about our personal experiences, including the "what", "when", and "where" of our daily lives (Tulving, 1972, 2002), and allows us to adapt our responses to present circumstances, imagine the future based on the past and create a concept of self (Clayton & Dickinson, 1998; Schacter, Benoit, & Szpunar, 2017).

The following experimental chapters will focus specifically on individuals' ability to remember object-location associations at different time intervals from encoding. For this reason, the memory systems probed as part of this thesis are visual WM and episodic LTM.

1.1 The distinction between WM and LTM

The WM-LTM dichotomy dates back at least as early as the 19th century. In his "Principles of Psychology", William James (1890) proposed that primary and secondary memory are qualitatively different (James, 1890). The equivalent of WM, he defined primary memory as stimulation from the present environment that has not yet left consciousness, whereas secondary memory referred to material stored indefinitely that can be retrieved to consciousness. Within modern cognitive psychology, these ideas were formalised in models proposed by Atkinson and Shiffrin and later by Baddeley and Hitch (Atkinson & Shiffrin, 1968; Baddeley & Hitch, 1974).

Studies of brain-lesioned individuals represented key evidence in favour of the dichotomy. They also suggested that the two memory systems are reliant on separate brain structures, as neuropsychological assessments indicated that injuries to different brain areas impaired LTM but spared WM, or vice versa (Milner, Corkin, & Teuber, 1968; Scoville & Milner, 1957; Shallice & Warrington, 1970; Warrington & Shallice, 1969). The influential case of patient HM, who underwent a bilateral partial temporal lobe resection to treat his recurrent epileptic seizures, is an example of medial temporal lobe damage (MTL) leading to severe LTM impairment. Post-operative neuropsychological examinations pointed towards a case of

anterograde amnesia, as HM was unable to form any new long-term memories following the surgery. Conversely, HM's WM remained relatively intact (Milner et al., 1968; Scoville & Milner, 1957). In contrast, patient K.F. suffered from impaired verbal WM, but spared LTM, as a consequence of a childhood motorcycle accident in which he sustained lesions to his left occipital and parietal lobes (Shallice & Warrington, 1970; Warrington & Shallice, 1969).

Behavioural evidence from studies of healthy cohorts also contributed to this dichotomous view of the two memory systems. These proposed the notion that WM and LTM were controlled by distinct mechanisms and that they encoded information differently. For example, when probing verbal WM, retrieving a list of words that were acoustically similar yielded more errors compared to words that were semantically alike (Baddeley, 1966a). On the other hand, a similar study probing LTM retrieval of word lists showed the contrary, that semantic resemblance led to more errors compared to acoustic similarity (Baddeley, 1966).

With the development of neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), more evidence complemented previous findings that supported the WM-LTM distinction. Although these views were disputed later (see section 1.2), these studies emphasised the contribution of mostly separate brain areas in the normal functioning of the two memory systems. Specifically, reinforcing conclusions post-HM, the MTL was shown to play a crucial part in both LTM encoding and retrieval (Schacter & Wagner, 1999). Separately, the prefrontal cortex (PFC) is key for WM, besides other modality-dependent areas (Braver et al., 1997; Owen, 1997).

For a long time, all this evidence propagated the idea that WM and LTM were two independent memory systems, contained within different brain areas, controlled by distinct mechanisms, and that stored information differently. Nevertheless, methodological advancements in the field, both at the behavioural level through the development of more sensitive tasks and regarding our understanding of neuroimaging techniques and analyses have challenged these views.

1.2 MTL – the common denominator

With time, questions arose regarding the neuropsychological studies that had established the verdict on the WM-LTM dichotomy, particularly when new imaging research aiming to pinpoint the seats of the two memory systems began to consistently show different results.

In a direct cross-function comparison between regions activated during WM and LTM using fMRI, Cabeza and colleagues (2002) found that both WM and LTM recruited MTL regions such as the hippocampus (Cabeza, Dolcos, Graham, & Nyberg, 2002).

The MTL is a system of functionally and anatomically connected structures: the amygdala, the hippocampus and the surrounding parahippocampal, perirhinal and entorhinal cortices, which form the biggest part of the parahippocampal gyrus. These structures have various subcortical and neocortical reciprocal connections, with the entorhinal cortex relaying most communication between the hippocampus and the cortex, which in turns gets its inputs from the parahippocampal and perirhinal cortices. That way the medial temporal lobe communicates with the frontal, temporal, and parietal lobes (Bird and Burgess, 2008). Its position in the brain gives the hippocampus an advantage for memory function, as it receives highly processed sensory information from all the principal sensory cortices. This information is passed to the hippocampus through the entorhinal cortex, which is generally sub-divided into medial and lateral portions. The lateral entorhinal cortex (lEC) receives sensory information from the perirhinal and olfactory cortices, while the medial entorhinal cortex (mEC) receives spatial information from the retrosplenial, parietal and occipital cortices, and these two pathways are often characterized as the 'what' and 'where' processing streams respectively (van Strien et al., 2009). Animal studies of memory have proposed theories of functional specialization within the MTL, whereas some studies in humans, especially in patients with neurological damage, suggest that the human MTL is a unitary memory system supporting all types of declarative memory, our conscious memory for facts and events

whereas others propose that the MTL has dissociable functions in memory (Barense et al., 2005).

This debate has been evident in studies aiming to establish distinctions between semantic and episodic memory. In a study of three patients with amnesia caused by hippocampal damage sustained, in two of the cases, very early in life, Vargha-Khadem and colleagues (Vargha-Khadem et al., 1997) found that they could classify their most pronounced impairments in three categories: spatial – they could not find their way in familiar environments, remember where objects are typically located, or where they placed them; temporal – they could not orient in date or time; episodic – they could not remember the day's activities or telephone conversations, stories, or vacations. Neuropsychological tests further identified significant impairments in remembering voice-face and object-locations associations. However, the patients' semantic memories were intact. The explanation proposed was that the difference in the two systems' impairment resulted from the fact that semantic memories can be stored partly independently of episodic memory. This theory suggests that the sensory memory roles of the perirhinal and entorhinal cortices may suffice to support semantic memories but not context-rich episodic memories, which therefore requires the additional hippocampal resources. According to this theory, semantic and episodic memory would be equally degraded in cases of anterograde amnesia, such as HM, when both the hippocampus and surrounding cortices are damaged (Vargha-Khadem et al., 1997). Several theories of MTL function are further discussed in sections 1.2.2.

Returning to the WM-LTM dichotomy, the fact that both memory systems recruited MTL regions was surprising at the time because a great body of neurophysiological, neuropsychological, and neuroimaging studies had previously established its critical role in LTM formation and retrieval, but not in WM (Cohen et al., 1999; Squire, 1992; Tanaka, 1997). What is more, MTL activations had been infrequent in earlier PET or fMRI studies of WM (for a review see Cabeza & Nyberg, 2000). Increasing evidence from electrophysiological and neuroimaging studies that consistently demonstrated MTL engagement in WM tasks ensued

(Ranganath & D'Esposito, 2005), despite earlier MTL lesion studies showing preserved WM. This evidence was not restricted to correlated MTL activations in healthy adults but was later complemented by lesion studies which allowed for causal inferences, indicating that the differences between more modern findings and earlier lesion studies may have stemmed from different study designs.

1.2.1 The associative role of the MTL

In a quest to explain these findings and the MTL's role in the functioning of the two memory systems, the relational-processing theory was key. This suggests that the MTL is crucial for encoding information previously defined as contextual (Hirsh, 1974), configural (Sutherland & Rudy, 1989), or relational (Cohen & Eichenbaum, 1993) and was supported by a growing body of literature indicating that an important function of this region is to establish novel associations within certain domains in declarative memory, due to the fact that it is part of a highly interconnected network. These may be within features of an object, such as size, colour, texture, shape, between objects, more integrative relationships such as between objects and their context, or higher-order relationships based on the temporal contiguity of objects and events. By forming associations among inputs, the MTL becomes crucial for the production, recombination, and adaptable use of information. Cohen and Eichenbaum (1993) stated that the MTL, particularly the hippocampus, supports memory by acting as a relation mechanism, across species, tasks, and modalities (Cohen & Eichenbaum, 1993). Their theory was based on and extended Wickelgren's (1979) view of the hippocampal role of chucking or creating "vertical associations", and on Damasio's (1989) view of the hippocampus as a "convergence zone" where co-occurrences of activity patterns are bound together (Damasio, 1989; Wickelgren, 1979).

According to this view, the involvement of the MTL is given by its associative abilities, rather than the timescale on which it operates, explaining its recruitment both in WM and LTM. Thus, earlier MTL lesion studies showing preserved WM may have reflected patients'

unimpaired abilities to retrieve information that did not involve binding or used methods that were not fine-tuned to these functions. There is growing evidence that associative memory is different from other, non-associative forms of memory (K. J. Mitchell, Johnson, Raye, & D'Esposito, 2000). Therefore, measuring WM for single features does not provide a complete view. If this theory is valid, then patients with MTL damage should in fact show impaired WM abilities when retrieval of associations is required.

Case in point, more recent studies have shown that MTL impairment, particularly to the hippocampus, does affect WM (Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Pertzov et al., 2013; Watson, Voss, Warren, Tranel, & Cohen, 2013; Zokaei et al., 2019b). For example, Olson and colleagues (2006) presented individuals with bilateral MTL damage with three objects within a nine-cell grid and, after a delay of either one or eight seconds, asked them to remember either the objects' identities, their locations or the object-location associations. Participants' associative WM was probed by asking them to respond whether the object in the retrieval array was in the same location as before the delay. Participants with MTL lesions showed worse memory for object-location associations compared to healthy participants, whereas their memory for individual features was unimpaired (Olson et al., 2006). Other studies that probed recall rather than recognition, using more sensitive continuous-report measures brought additional evidence of MTL involvement in WM. These typically required participants to place a target item back to its original encoded location and calculated participants' proportions of swaps from their responses to measure their associative abilities. Their findings showed that individuals with MTL lesions, regardless of lateralisation or aetiology, placed target stimuli in the location of non-target items previously encoded more frequently compared to healthy individuals, making significantly more mis-binding errors (Pertzov et al., 2013; Watson, Voss, Warren, Tranel, & Cohen, 2013; Zokaei et al., 2019). The differences in localisation errors between healthy and impaired individuals were fully explained by their mis-binding proportions, while location memory was equally precise between the two groups when one item had to be recalled at a time (Pertzov et al., 2013; Zokaei

et al., 2019). These studies support the view that the MTL plays a role in memory as an associative mechanism.

Neuroimaging studies also complemented the behavioural evidence of MTL involvement in associative WM. For example, using a multivoxel pattern similarity analysis, Libby et al. (2014) found that voxels in the right hippocampus displayed increased pattern similarity during the encoding and maintenance of item-location associations in correct, but not incorrect trials, indicating that the hippocampus plays a key role in the effective encoding and maintenance of these relations (Libby, Hannula, & Ranganath, 2014). Participants were asked to encode the identities and locations of four different everyday objects within a three-by-three grid. Following the 11 second delay, a probe grid rotated by 90 degrees compared to the original was presented. A third of the probe grids preserved the object-location associations encoded (match condition), a third showed the same four objects occupying the same four locations, except that two objects' positions were swapped (mismatch-swap condition), and the rest presented the same four objects, but one object's location was changed by one cell (mismatch-position condition). Participants were asked to indicate the condition type. Therefore, their performance was highly reliant on their familiarity with the object-location associations, ensuring that the task would activate brain areas responsible for their encoding and retrieval (Libby et al., 2014).

1.2.2 MTL and spatial memory

Although not exclusively, most studies that confirmed the role of the MTL in associative memory regardless of timespan focused on associations with a spatial component. One proposed explanation brings into the spotlight another key function of this structure.

Once the MTL was declared the seat of memory following HM's case, it became the centre of an extensive body of research. Among the discoveries, the hippocampus was specifically shown to modulate our perception of space. It all started with the discovery of "place cells." Fifty years ago, O'Keefe and Dostrovksy (1971) defined these as hippocampal

neurons that fire when a rat is in a particular location in the environment (O'Keefe & Dostrovsky, 1971). Later, several other spatially modulated cell types were discovered within the MTL, such as grid cells, head direction cells, border cells, and speed cells (Kropff, Carmichael, Moser, & Moser, 2015; Shine, Valdés-Herrera, Hegarty, & Wolbers, 2016; Solstad, Boccara, Kropff, Moser, & Moser, 2008; Taube, 2007). There is now abundant evidence of the existence of these cells in several mammalian species from humans and non-human primates to mice and bats, demonstrating that the MTL plays a crucial part in spatial representation and memory (Ekstrom et al., 2003; Feigenbaum & Rolls, 1991; McHugh, Blum, Tsien, Tonegawa, & Wilson, 1996; Ulanovsky & Moss, 2007).

What is more, within the field of spatial navigation, two types of spatial representations were defined: egocentric representations, encoding the placement of stimuli within the environment in relation to the self, and allocentric representations, which rely on associations between stimuli, as they refer to their location relative to each other, independent of self within the external environment (Burgess, Spiers, & Paleologou, 2004; Colombo et al., 2017; Howard & Templeton, 1966; A. D. Milner & Goodale, 1992). A great body of literature exploring the neurobiological mechanisms of the two navigational frames has reached consensus on the findings that the allocentric frame is primarily guided by the hippocampus and parahippocampal cortex, whereas the egocentric frame relies mainly on the striatal system (Aguirre, Detre, Alsop, & D'Esposito, 1996; Cook & Kesner, 1988; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; J. O'Keefe & Dostrovsky, 1971).

With time, several theories about the role of the MTL, and specifically the hippocampus, beyond human recollection have emerged, initially rooted in its spatial memory role, and later considering a wider function. First, cognitive map theory proposed that this structure plays a critical part in encoding, maintaining and remembering spatial information, particularly of the allocentric kind (John O'Keefe & Nadel, 1978). Later, Nadel and Moscovitch (1997) came up with the multiple trace theory that stated that the hippocampus mediates episodic, but not semantic memory retrieval and that it is activated primarily, if not

exclusively, by spatial contextual information (Nadel & Moscovitch, 1997). In contrast, Eichenbaum and Cohen proposed that the MTL's role in all spatial and navigational operations is merely an example of the way this structure specialises in forming associations. Their relational theory postulates that this structure is key for all types of associations and episode sequences that form our everyday lives, regardless if spatial or non-spatial content is involved, extending to both episodic and semantic domains (Cohen & Eichenbaum, 1993; Eichenbaum, 2004). They claim that this theory also encompasses the process of acquiring semantic associations as this knowledge has been conceptualised as being in the form of semantic networks and, in support, propose the following scenario: perceiving an item in an environment, activates nodes corresponding to that item, which in turn spreads through the connections activating ideas of similar items based on semantic knowledge and networks. They argue that the contribution of the hippocampus to spatial processes stems from its general role in memory necessary for successful navigation rather than from performing navigational operations per se (Eichenbaum & Cohen, 2014).

To address this long-standing debate regarding the function of the MTL, and particularly of the hippocampus, Kumaran and Maguire (2005) used fMRI and a task in which the relational abilities required to navigate in a spatial context were matched with similar relational processing involved in navigating nonspatial (social) domains (Kumaran & Maguire, 2005). They found that hippocampal activity was biased towards spatial and navigational processing, consistent with the cognitive map theory. The task involved two conditions, one relational and one non-relational, and each had both spatial and social demands. Two weeks prior to the experiment, participants provided information on 14 of their friends that was used as stimuli. Participants were presented with eight of their friends' names and told that the person at the top left of the name array had to give the person at the top right of the array a crate of wine. For the social condition, the receiver must know the giver for the transaction to take place, whereas in the spatial condition, the receiver must live closer to the person at the top right of the array. Participants were asked to calculate the maximum number of wine bottles that could be removed from the crate until it reaches its destination (the friend at the

top right of the array), as each time a transaction was made, a bottle was removed. On the other hand, in the non-relational condition, participants were presented with a similar array of eight names and were asked to determine how many of them wore glasses (social) or lived in a particular type of building (spatial). Despite similar behavioural performances, the findings showed distinct patterns of neural activation. Significantly, the hippocampus and parahippocampal cortex were exclusively activated by spatial relational tasks, as proposed by the cognitive map theory (Kumaran & Maguire, 2005). However, one aspect must be considered when interpreting these findings. Specifically, the social and spatial demands of the relational condition might have relied on different levels of relational processing, even though they were comparable in terms of difficulty and time requirements. In this sense, it has been previously demonstrated that the amount of relational processing necessary to perform a memory task modulates hippocampal activity (Cohen et al., 1999).

More recently, Ryan and colleagues (2010) set the same goal of determining which of the three theories of MTL function, and specifically of the hippocampus, is correct. They investigated MTL activations related to spatial and non-spatial relational tasks of episodic and semantic memory. Using fMRI and an elegant paradigm relying on equivalent stimuli and measures across conditions, they found partial evidence in support of all three theories. Participants were asked to remember the identities and locations of common objects presented as photos, cartoons or line drawings within four-cell arrays. During retrieval, participants were asked questions from seven conditions including all combinations of spatial/non-spatial and episodic/semantic areas and a control condition. In accordance with the cognitive map theory (O'Keefe & Nadel, 1978), their findings showed that MTL regions were activated to a greater extent by spatial compared to non-spatial relations. Additionally, they found that spatial relational activations had a more posterior distribution. Consistent with the multiple trance theory (Nadel & Moscovitch, 1997), they also observed a higher degree of MTL engagement for episodic compared to semantic retrieval. Lastly, supporting the relational theory (Cohen & Eichenbaum, 1993), they found that, in fact, all conditions activated the MTL. Nevertheless, the degree of engagement and its location along the anterior-

posterior hippocampal axis was characteristic for the type of associative operation (spatial/non-spatial) and the kind of information (episodic/semantic). Specifically, they found greater activation for spatial compared to non-spatial, and for episodic compared to semantic relations.

1.3 WM and LTM in healthy ageing

Another aspect the two memory systems have in common, besides their MTL-supported associative mechanisms, is the fact that they both decline with normal healthy ageing. Deficits in memory function are among the most encountered complaints of old individuals. However, the causes, rates and features of this deterioration might be different between the two systems.

First, research using sensitive continuous-report measures has shown that WM becomes less precise with ageing, with old adults making larger errors in equivalent measures compared to young individuals (Peich, Husain, & Bays, 2013; Pertzov, Heider, Liang, & Husain, 2015; Zokaei, Grogan, et al., 2020). However, associative deficits in WM in healthy old adults are still under debate (Allen, Brown, & Niven, 2013; M.-C. Peich et al., 2013; Pertzov et al., 2015). Previous work relying on the retrieval of object-location associations has yielded mixed results (Lugtmeijer, de Haan & Kessels, 2019). Although numerous studies have revealed older adults' increased probability for mis-binding the location of target and non-target objects (Cowan, Naveh-benjamin, Kilb, & Saults, 2006; Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000; Peich, Husain, & Bays, 2013), others do not identify any differences between young and old adults in their retrieval of associations (Bopp & Verhaeghen, 2009; Read, Rogers, & Wilson, 2016). Moreover, when old individuals are instructed to form associations between objects' surface features, there is also little or no evidence for an age-related relational deficit (Brockmole & Logie, 2013; Parra, Abrahams, Logie, & Sala, 2009).

Similarly, studies using continuous-report measures have also showed decreased LTM precision in old adults reflected by greater errors compared to young individuals (Korkki, Richter, Jeyarathnarajah, & Simons, 2020; Salvato, Patai, & Nobre, 2016a). It is important to note that, although influential theories aiming to explain memory decline in ageing focus on deficits in relational abilities (Naveh-Benjamin, 2000; Naveh-Benjamin & Mayr, 2018), other studies using similar continuous-report measures have also identified that memory resolution for single objects also declines with age (Zokaei, Sillence, et al., 2020). These findings could point towards divergent mechanisms of age-related decline between WM and LTM.

Behavioural changes caused by healthy ageing have also been found to be accompanied by anatomical and functional deterioration of the brain. Several neuroimaging studies have proposed that the prefrontal cortex (PFC), initially known to play a role in WM, the MTL, and sensory areas may flexibly interplay during encoding, maintenance and retrieval of both WM and LTM (Axmacher, Schmitz, Wagner, Elger, & Fell, 2008; Jenkins & Ranganath, 2010; Kim & Cabeza, 2007; Ranganath, Cohen, & Brozinsky, 2005; Simons & Spiers, 2003). Healthy ageing could possibly change the structure and function of these brain areas and, consequently, their functional relationships, leading to changes in WM and LTM.

An age-related decrease in MTL volume has been previously correlated with LTM decline in both cross-sectional and longitudinal studies (Gorbach et al., 2017; Henson et al., 2016) possibly justifying an increased rate in mis-binding errors in old adults (e.g., Peich, Husain, & Bays, 2013; Zokaei et al., 2020). What is more, changes in fMRI blood-oxygen-level-dependent (BOLD) signal have been found in the hippocampus, indicating a decrease in functional recruitment for old adults (Pudas et al., 2013). The same study showed that elderly individuals with preserved performance demonstrated increased hippocampal BOLD signal instead (Pudas et al., 2013). What is more, preserved performance in old age was found to correlate with increased functional recruitment of the PFC (Pudas et al., 2013). Separately, other LTM imaging studies have shown that old adults' retrieval is highly susceptible to interference from extraneous information, possibly caused by decreased control mediating the

selection of relevant details (Wais & Gazzaley, 2014). Wais et al. (2012) examined older adults' memory recall abilities when their eyes were either closed or open and irrelevant information was shown. They also compared their results to those of an earlier identical study performed on young participants. Their findings suggest that unrelated visual stimuli reduced old individuals' LTM retrieval abilities and that visual distraction impaired retrieval to a greater extent in older compared to younger adults. These findings point towards a declining mechanism of selective LTM retrieval with increasing age (Wais, Martin, & Gazzaley, 2012).

Imaging studies of WM in old age have described correlations between age-related reductions in PFC volume and decreased inhibition of distractions during WM tasks (Zanto & Gazzaley, 2019). Likewise, reduced functional recruitment of the PFC in older adults has been connected to reduced WM retrieval performance (Yaple, Stevens, & Arsalidou, 2019). Conversely, a compensatory mechanism has been identified in older adults with preserved performance manifested as increased functional recruitment of the PFC (Toepper et al., 2014). However, most of this research relies on simple categorical stimuli within paradigms such as n-back or delayed match-to sample. Therefore, these structural and functional changes might insufficiently explain the observed age-related deficits in the retrieval of more complex representations in WM.

1.4 Memory and limbic encephalitis

Research centred around healthy ageing enables an understanding of the natural progression of the patterns of WM and LTM. However, these studies are constrained in how much they can elucidate the mechanisms underlying age-related changes. As a result, studies that investigate a clinical cohort with known impairments become an instrumental source of evidence on the interplay and differences between the two memory systems.

As discussed previously, earlier literature has consistently demonstrated that, despite not being entirely coextensive, both WM and LTM rely on medial temporal lobe (MTL) and hippocampal integrity for normal functioning. For this reason, considering their focal MTL

damage, patients with limbic encephalitis (LE) represent a unique opportunity to elucidate the dependence of the two memory systems on the MTL, and thus help clarify the nature of the relationship between WM and LTM for the same type of stimuli.

LE was first described in 1960 by Brierley and colleagues as a series of three clinical cases (Brierley, Corsellis, Hierons, & Nevin, 1960). Yet, the pathogenesis remains elusive due to the symptom heterogeneity. One of the main markers of LE in the acute phase is severe anterograde amnesia, typically accompanied by other symptoms such as anxiety, depression, irritability, personality changes, confusion, hallucinations, and complex partial and secondary generalised seizures. Advancements in neuroimaging tools and identification of antineuronal antibodies in patients with LE have enabled earlier identification of the disease (Anderson & Barber, 2008). LE associated with antibodies to the voltage-gated potassium channel complex (VGKC) is one of the most common forms of the disease. Patients usually respond well to treatment and in the post-acute phase, most symptoms subside, apart from memory deficiencies. Lastly, the T2 hyperintensities on the MRI in the acute phase lead to MTL atrophy in the post-acute phase of the disease (Argyropoulos et al., 2019; Butler et al., 2014).

The WM abilities of individuals with LE have been previously assessed using a visual WM task with a sensitive, continuous measure of report and showed that they made larger errors when several items had to be remembered, but not for a single items, compared to healthy controls (Pertzov et al., 2013). Separately, LTM impairment in individuals with LE has been apparent in several studies using a broad range of tests. Using a comprehensive neuropsychological test battery to assess cognitive function longitudinally in participants with LE, Butler et al. (2014) showed that they may experience permanent LTM deficits despite cognitive domains being preserved (Butler et al., 2014). More recently, Argyropoulos et al. (2019) characterised an LE cohort and found that they showed pronounced episodic memory retrieval impairment of both verbal and visual material (Argyropoulos et al., 2019).

1.5 Measuring MTL-based memory

1.5.1 Sensitive measures

To obtain a complete picture of the dichotomy, similarities, and interplay of WM and LTM mechanisms, the study of special populations is not the only important aspect. In this respect, choosing the most sensitive, relevant measures and methodologies becomes key to filling the gaps in our current understanding, particularly when considering challenges imposed by healthy ageing discussed thus far.

Within WM literature, the capacity of this memory system has been traditionally quantified using 'span' measures obtained by asking individuals to learn and remember a sequence of stimuli (e.g., letters) in the same order (Groeger, Field, & Hammond, 1999). However, WM function goes beyond information maintenance and involves additional manipulation and information processing. Typically, to measure the effects of these operations, studies have used backwards span tasks asking participants to remember sequences of stimuli in reverse order (Miller, Price, Okun, Montijo, & Bowers, 2009). These paradigms have been deemed to be reliable measures of WM storage and additional processing abilities (Conway et al., 2005; Cornoldi & Mammarella, 2008), and neuroimaging studies have confirmed the fact that they tap into different aspects of WM (Fletcher & Henson, 2001; Postle, Berger, & D'Esposito, 1999). Despite their seminal role in advancing our understanding of memory systems, such measures of performance might not be sufficiently sensitive to perceive changes in memory resolution. A characteristic of these paradigms is that they rely on "all-or-none" binary measures, meaning that participants can either give a correct or incorrect answer. However, an error on binary choice of stimuli does not imply no memory of an item at all. Similarly, a correct choice does not reflect the resolution of the respective memory (Ma, Husain, & Bays, 2014).

For this reason, an alternative approach to measure WM abilities was developed that focuses on the precision with which stimuli are retrieved from WM. Delayed adjustment tasks ask participants to replicate the target features of maintained items (Gorgoraptis, Catalao,

Bays, & Husain, 2011; Ma et al., 2014; Zokaei, Heider, & Husain, 2014). For example, individuals are showed a sequence of oriented coloured bars and then asked to replicate the exact orientation of the probed bar after a delay. To investigate whether these precision measures provide a more sensitive estimation of WM abilities, Zokaei and colleagues (2015) used a delayed adjustment task where participants were presented with a series of either three or four oriented coloured bars. After a short delay, they were asked to match the orientation of the probe bar to that of the same-coloured bar previously encoded. They compared participants' performance on this task to their performance on both a forwards and a backwards digit span task. Their findings showed that span measures correlated with participants' precision across the life span. What is more, they found that measures of precision might be a more sensitive method to explore WM abilities, particularly in impaired populations (Zokaei, Burnett Heyes, Gorgoraptis, Budhdeo, & Husain, 2015).

Separately, but similarly, typical LTM research measures individuals' abilities using categorical variables, for example asking participants to determine whether a target item has been encoded previously or not (old/new). As in the case of WM, these methods only allow for binary separation between correct and incorrect retrieval and do not tap into the more complex mechanism of LTM. Growing evidence proposed that LTM retrieval also relies on a "some-or-none" mechanism where retrieval resolution can fluctuate and reveal the memory quality (Harlow & Donaldson, 2013; Korkki et al., 2020; Yonelinas & Parks, 2007). To put these assumptions to test, more recent work has focused on continuous-report measures of retrieval, using tasks that ask participants to reproduce features of target items using analogue scales. In fact, several studies have shown that retrieval success and precision are discrete components of LTM (Harlow & Donaldson, 2013; Harlow & Yonelinas, 2016; Richter, Cooper, Bays, & Simons, 2016). Moreover, one study also demonstrated that these two constructs also dissociate at a neural level, as they depend on separate regions of the episodic memory network (Richter et al., 2016). Therefore, considering their established dissociation in young adults, they may benefit studies aiming to uncover the mechanisms of age-related memory decline as they may detect changes with different sensitivities.

Importantly, these methods, applied both in studies of WM and LTM, enable the examination of MTL-based associative mechanisms and hence of the interplay and dissociations of the two memory systems. They also open up new possibilities to explore the patterns of errors by identifying their sources using computational modelling (Bays, Catalao, & Husain, 2009; Grogan et al., 2020; Zokaei et al., 2014).

1.5.2 Sensitive methods

In our daily lives, associative abilities, specifically those involving a spatial component don't only come into play in static contexts that only require us to remember the location of an object limited by our field of view. Instead, we typically encounter more complex tasks that demand us to navigate to a remembered location. For this reason, to increase the ecological validity and reliability of our results, we need to choose appropriate methods, particularly when considering the needs of a special population such as ageing adults. Research involving spatial cognition advanced with the introduction of virtual-reality (VR) technology. This refers to computer-simulated 3D environments where participants can navigate, independent of the viewing condition – that is, on a computer screen or in an immersive way using a head-mounted display. What is more, VR studies enable access to more realistic examination of participants' abilities through such testing environments. The use of VR for measuring older adults' memory abilities is still in its infancy. So far, studies suggests that the effects of age on spatial abilities are comparable between VR and real-world tasks, opening up new possibilities for more sensitive methodologies to examine spatial memory of older adults (Diersch & Wolbers, 2019; Taillade, N'Kaoua, & Sauzéon, 2016).

1.6 Attention – a modulator of memory performance

When trying to paint the complete picture of the WM and LTM retrieval mechanisms, these systems' interaction with other modulatory cognitive process has also been a fruitful

avenue for exploration. Particularly, the parallel between selective retrieval and selective attention proved effective. This was drawn by Chun and Johnson (2011) who suggested that attention could be characterised according to the direction of deployment, in internal or external attention (Chun & Johnson, 2011) after observing similarities between the use of selective attention in searching for objects in the external world and internally, in memory.

Previously, studies of spatial attention have shown that providing an informative predictive cue (pre-cue) that indicates the location a target stimulus will most likely occur increases the detection rate and improves participants' ability to discriminate its identity (Posner, 1980). This paradigm, commonly referred to as the Posner cueing task (Posner & Petersen, 1990), has been fundamental to numerous behavioural studies of attention. Later, research adapted the Posner paradigm and introduced the concept of retro-cues, a new tool for investigating whether individuals could orient attention internally to improve retrieval of selected items or features from memory. Griffin and Nobre (2003) used a change-detection paradigm to compare WM performance when spatial pre-cues and retro-cues were provided, and to determine whether top-down selective attention could improve WM retrieval (Figure 1.1). Participants were presented with a memory array consisting of four coloured X's located in the four quadrants of the screen. In the pre-cue condition, they were then shown a spatial pre-cue that indicated the location of one of the encoded stimuli that would most likely be probed with 80% validity. After a short delay, the probe item appeared and participants were asked to respond whether the item was previously seen in the encoding array (Experiment 1), or whether it was previously in the cued location (Experiment 2 and 3). In the retro-cue condition, after seeing the memory array, participants were shown a spatial retro-cue, indicating which item was likely to be probed. The retro-cue condition had the same retrieval demands as the pre-cue condition. Lastly, the neutral cue condition did not provide any predictive cues to narrow down the amount of information retained. The results showed that performance was improved when valid pre- and retro-cues were available compared to the absence of predictive cues, which was in turn better than performance during invalid cued conditions. Importantly, these results established that individuals can use retro-cues to orient

attention internally within WM and enhance their retrieval performance (Griffin & Nobre, 2003; see also Landman, Spekreijse, & Lamme, 2003). Since then, numerous subsequent studies have reliably replicated these results (e.g., Lepsien, Griffin, Devlin, & Nobre, 2005; Lepsien, Thornton, & Nobre, 2011; Makovski & Pertzov, 2015; Murray, Nobre, Clark, Cravo, & Stokes, 2013; Myers, Walther, Wallis, Stokes, & Nobre, 2015; Souza & Oberauer, 2016; Souza, Rerko, & Oberauer, 2016; Wallis, Stokes, Cousijn, Woolrich, & Nobre, 2015)

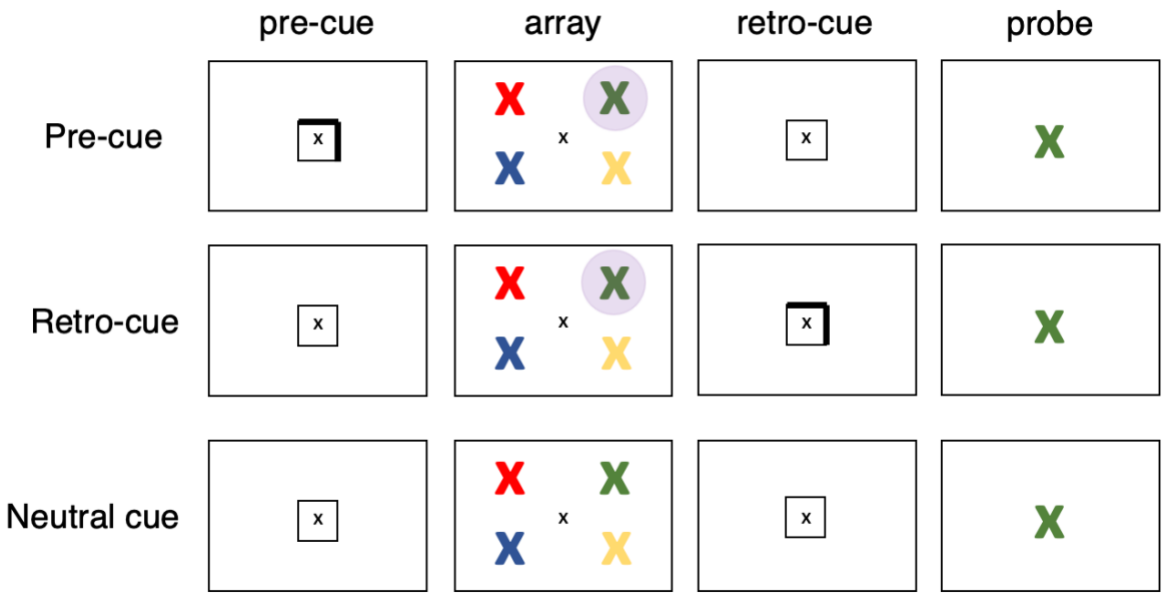

Figure 1.1 This schematic of the task from Griffin and Nobre (2003) illustrates the timeline of one trial of the task for each of the three conditions (pre-cue, retro-cue and neutral cue). In the pre-cue condition (top), a spatially informative cue (80% valid) was shown, followed by the memory array. In the retro-cue condition (middle), the spatially informative cue (80% valid) followed the presentation of the memory array. The neutral cue trials (bottom) did not provide predictive cues. Participants were probed to respond whether the stimulus shown at the end of each trial in the centre of the screen was present in the encoded memory array (Experiment 1). In a second experiment, the probe item appeared in one of the four quadrants of the screen and participants were asked to respond whether the location matched its original one in the memory array. Lastly, during a third experiment with only pre- and retro-cue trials, the probe was shown at the centre and participants had to report whether it previously appeared at the cued location. This schematic design was adapted from Griffin and Nobre (2003).

Returning to the dichotomy between WM and LTM, these findings uncover an unexplored area of their relationship and possible similarities, and lead to a question that

remains unanswered. Do retro-cues also benefit LTM retrieval? Earlier retro-cueing findings reveal an opportunity to answer numerous research questions that aim to uncover the relationship between and mechanisms underlying attention and memory of different timespans. In beginning to hypothesise about the answers to this question, the different underlying mechanism of WM retro-cue benefits, as well as existing knowledge of selective attention in LTM should be considered.

Keeping in mind the importance of continuous-report measures, it is relevant to note that WM studies have previously observed that retro-cued information is not only retrieved quicker and more accurately, but they also demonstrated that orienting attention internally during WM also improved precision with which features are retrieved (e.g., Gunseli, van Moorselaar, Meeter, & Olivers, 2015; Makovski & Pertzov, 2015; Souza & Oberauer, 2016). On the other hand, non-cued items have been shown to erode in the quality of their retrieval (LaRocque et al., 2015). Questions arise whether retro-cueing in LTM would also improve retrieval of target items and degrade the quality of unattended ones. Related evidence so far comes from earlier research using the Think/No Think paradigm which found the memory for selected-against items decreases (Anderson & Hanslmayr, 2014).

Another good starting point for establishing predictions regarding retro-cueing mechanisms in LTM is the Attention To Memory (AToM) theory which suggests that the internal deployment of attention during retrieval may emulate the external orienting of attentional selection (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Ciaramelli, Grady, & Moscovitch, 2008). What is more, Duncan et al. (2012) showed that the response of the hippocampal subfield CA1 acts as a match/mismatch detector modulated by the relevance of the dimension attended (Duncan, Ketz, Inati, & Davachi, 2012). These results support the idea that, in theory, selective attention can also modulate processes or activity underlying LTM retrieval. However, despite these theoretical accounts supporting the idea that LTM retrieval can also be considered an act of selective attention within countless stored memories, there is no effective experimental approach that focuses on orienting attention to contents in LTM.

1.7 Aims of the thesis

The evidence discussed in this section confirms that WM and LTM are not as different as previously thought. Although some distinctions remain, others were in fact confounds of measuring, describing, and comparing the two memory systems using different methodologies, tasks and stimuli. Acknowledging their differences, but guided by their similarities, this thesis focuses on MTL-based WM and LTM. The studies presented in the upcoming chapters explore their mechanisms and interplay based on their common associative mechanisms, with a focus on spatial associations, using analogous tasks and equivalent behavioural measures. They also investigate the modulatory relationship between the two memory systems and attention. What is more, one solution for identifying a complex view of their differences and similarities is to investigate the abilities of individuals who suffer from degraded WM and LTM, such as healthy older adults and individuals with pathological memory loss. If the mechanisms underlying the two memory systems are overlapping, then both will show similar impairment, as well as a preserved relationship. Conversely, if sufficiently different mechanisms support the two memory systems, they will be differently affected, and their relationship might erode with time.

To this end, Chapter 2 explores whether retro-cueing benefits extend to LTM retrieval, and whether this could represent a means of ameliorating age-related LTM degradation. Additionally, this chapter also considers whether young individuals' abilities to benefit from retro-cues correlates between the two memory systems, and whether this is preserved with ageing. This work is based on two equivalent retro-cueing memory tasks that incorporated measures of both object identification and object-location associations in WM and LTM. Next, in Chapter 3, I first compared the performance of young and older healthy adults in a spatial memory task on two devices – a personal computer and an immersive VR device – and measured whether elderly individuals benefit from an increased level of immersion, to determine the optimal methods of measuring spatial memory. Building on knowledge acquired in this study, I then used a spatial memory task within a navigational setting that

incorporated measures of both WM and LTM, to investigate the patterns of dissociation and interplay that might change with ageing. Lastly, Chapter 4 relies on the same navigation-based task to measure and compare WM and LTM in two groups of elderly individuals, one healthy and one with LE, aiming to analyse patterns of performance modulated by different levels of MTL impairment.

2. Attention-modulated retrieval in ageing

Abstract

Although not entirely coextensive, WM and LTM are not as different as once believed and there is consensus that they both decline with ageing. Stemming from the parallel between selective retrieval and selective attention, earlier research has established the positive modulating effect of attention on WM retrieval in both young and old adults. However, these effects have not been investigated in LTM. For this reason, this study explored whether these retro-cueing benefits extend to LTM retrieval and if this could represent a way of attenuating LTM retrieval decrease in old age. Capitalising on the equivalent tasks used to measure the two memory systems, I also investigated whether young and old individuals' abilities to use retro-cues correlate between the two memory systems, and whether this is preserved with ageing. For this, I developed equivalent retro-cueing memory tasks relying on measures of both object identification and object-location binding in WM and LTM. The results showed that, despite the negative ageing effects on both memory systems, both age groups retain the ability to use internal selective attention to benefit different features of their WM and LTM retrieval. Lastly, the patterns of retro-cues used seem to differ between the two memory systems, and their relationship is changed by the passing of time.

2.1 Introduction

Our external world inundates our senses with information that our brain is then tasked to filter based on our goals. Similarly, we store countless details of our everyday experiences in memory. For example, to remember where we left our keys before leaving the house, we need to search through all related material stored. There is simply too much information to be considered all at once. Instead, both perception and retrieval must be selective (Chun, Golomb, & Turk-Browne, 2011). This way, selecting information based on what is relevant to accomplish our tasks becomes a critical process supporting effective cognitive performance.

It is well established by now that retrieval abilities decline with age (Bopp & Verhaeghen, 2009; Chalfonte & Johnson, 1996; Fukuda & Vogel, 2019; Korkki, Richter, Jeyarathnarajah, & Simons, 2020; Lugtmeijer, de Haan, & Kessels, 2019; Naveh-Benjamin, 2000; Pertzov, Heider, Liang, & Husain, 2015; Salvato, Patai, & Nobre, 2016). Along with the deterioration of the anatomy and physiology of the brain, our abilities to retrieve information previously encoded to reach our goals also decrease (Daselaar, Dennis, & Cabeza, 2007). This is the case for memories of different time scales. Specifically, memories from the recent past, working memory (WM), and long-term memory (LTM) show declines with healthy aging (Chalfonte & Johnson, 1996; Fukuda & Vogel, 2019; Gazzaley, Sheridan, Cooney, & D'Esposito, 2007; Lugtmeijer et al., 2019; Naveh-Benjamin, 2000; Pertzov et al., 2015; Wais et al., 2012).

Deficits in WM can sometimes reflect deficits in prioritising relevant information or in avoiding the detrimental effect of distractions. Using a delayed-recognition and recall task in which both the encoding and delay period were manipulated, Gazzaley and colleagues (2007) found that age-related deficits may be due to decreased top-down attentional processing and to elderly adults' inability to suppress irrelevant information. They found that older individuals show a significant decrease in accuracy on the delayed-recognition task when maintenance was interrupted by a distractor (Gazzaley et al., 2007). What is more, in an fMRI experiment, Gazzaley et al (2005) showed that older adults struggle to inhibit irrelevant information during working memory maintenance. Specifically, younger and older individuals were presented with sequences of faces and scenes and were asked to remember the stimuli from one category while ignoring stimuli from the other category. However, the researchers only found BOLD activity decrease for the ignored stimuli relative to baseline in young participants, indicating that older adults were not able to suppress irrelevant information (Gazzaley, Cooney, Rissman, & D'Esposito, 2005). Separately, investigating two possible compensatory tactics that older adults might use to ameliorate the age-related decline in WM performance, Mitchell and Cusack (2018) found that when participants were shown the context of non-target stimuli seen at encoding in the retrieval phase, WM retrieval improved

for both young and old adults. Their findings indicate that, in fact, older individuals' capacity to benefit from deploying attention to external context and improve their memory abilities is preserved (Mitchell & Cusack, 2018).

Accurate retrieval of complex memories from our daily lives relies not only on the recall of individual memory features, but also of the relationships between them. However, the age-related associative deficits in WM are still under debate (Allen et al., 2013). Studies that instruct participants to retain object-location associations have yielded mixed results (Lugtmeijer et al., 2019). While several studies have revealed older adults' increased probability for mis-binding the location of target and non-target objects (Cowan, Naveh-benjamin, Kilb, & Saults, 2006; Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000; Peich, Husain, & Bays, 2013), others do not identify any differences between young and old adults in their retrieval of associations (Bopp & Verhaeghen, 2009; Read et al., 2016). For example, considering the role of such contextual associations, Pertzov and colleagues (2015) tested whether object-location binding was negatively influenced by aging in WM. They used an object-location task in which participants were presented with either one or three fractal objects for a period of 1 or 3 seconds and were instructed to remember both the objects' identities and their locations. After a delay of either 1 or 4 seconds, they were asked to choose between two objects, one of which was presented previously and the other was a lure, and then drag it to its remembered location using their finger. Their findings indicate a decrease both in object identification and in localization performance for older adults, but no changes in object-location association retrieval with increasing age (Pertzov et al., 2015). Additionally, when participants are instructed to form associations between the objects' surface features, there is also little or no evidence for an age-related binding deficit (Brockmole & Logie, 2013; Parra et al., 2009).

Separately, LTM studies have shown that elderly individuals' retrieval is more susceptible to interference from extraneous information, possibly caused by decreased control mediating the selection of relevant details (Wais & Gazzaley, 2014). Wais et al. (2012)

examined older adults' memory recall abilities for visual stimuli when their eyes were either closed or open and irrelevant information was shown. They also compared their results to those of an earlier identical study performed on young participants. First, they showed that unrelated visual stimuli reduced elderly participants' LTM retrieval abilities. Additionally, the comparison showed that visual distraction impaired retrieval to a greater extent in older than younger adults. These findings point towards a declining mechanism of selective LTM retrieval with increasing age (Wais et al., 2012).

Other studies of LTM retrieval proposed that age-related decline is caused by deficits in recalling associative information. Chalfonte and Johnson (1996) presented young and old participants with arrays of coloured objects and asked them to encode either the colour, location, or identity of the objects. Individuals' recognition memory for the features they were instructed to study was tested. They found that older adults showed a significant deficit in recognition memory for location and bound information, but not for item or colour compared to younger adults (Chalfonte & Johnson, 1996). Their findings have been consistently replicated (Kessels, Hobbel, & Postma, 2007; Naveh-Benjamin, 2000; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003). For example, Kessels et al. (2007) tested young and elderly participants using a computer-based memory task measuring memory for object identities, for locations and memory for the associations of the two features. Their findings showed significant age-related deterioration in the associative condition (Kessels et al., 2007).

As indicated by these studies, age-related memory deficits could stem from a combination of sources such as from a decline in selective attention, inability to cope with distractors, and a failure to form associations over time. At the same time, the two memory systems could erode differently over time, and their relationship could also fade with ageing (Lugtmeijer et al., 2019). So far, they have mainly been tested in isolation. However, using different tasks and measures to quantify WM and LTM could introduce difficulties when drawing comparisons and evaluating their relationship. As such, comparing WM and LTM

using equivalent tasks measuring identical variables becomes particularly important as it could reveal different patterns of decline with ageing. Additionally, this could also enable investigating different effects of top-down modulatory processes on the two memory systems and their development with time.

In the search for positive modulators of memory retrieval, the parallel between selective retrieval and selective attention proved fruitful. Noticing similarities between the use of selective attention in searching for objects in the external world and in memory, Chun and Johnson (2011) suggested that attention could be categorised according to the direction of deployment, in internal or external attention (Chun & Johnson, 2011). They further proposed that memory encoding could represent extended traces of external, perceptual attention, whereas retrieval was a result of internal, reflective attention (Chun & Johnson, 2011).

Stemming from the previously observed relationship between memory and attention, the solution was inspired by the seminal Posner cueing paradigm aiming to explore the orienting of attention outwards, in the perceptual domain. This task consisted of spatial cues guiding attention towards the location where a target stimulus would occur. The results showed improved detection and processing of the target, as revealed by faster reaction times and more accurate responses at the cued location (Posner, 1980).

Until recently, selective attention was only studied in the context of external deployment, and WM was considered to be impervious to this process after Sperling (1960) found post-cues to be ineffective at improving performance (Sperling, 1960). However, this theory was challenged by the introduction of retro-cues (Griffin & Nobre, 2003; see also Landman, Spekreijse, & Lamme, 2003). These provide predictive retrospective information about the target to be retrieved. Griffin and Nobre (2003) first presented participants with a memory array. Following a short delay, a spatial retro-cue appeared, predicting the location of the to-be-probed item. Lastly, participants were asked whether the colour of the probe item matched one of the objects previously presented at the same location. They found that retro-cues conferred a significant benefit for WM retrieval (Griffin & Nobre, 2003).

Since then, the retro-cueing effect has been consistently replicated (Souza & Oberauer, 2016). To date, studies investigating this effect using continuous measures have replicated improved retrieval accuracies of the retro-cued information (e.g., Makovski & Pertzov, 2015; Souza & Oberauer, 2016; Souza, Rerko, & Oberauer, 2016; Wallis, Stokes, Cousijn, Woolrich, & Nobre, 2015). Additionally, the neural underpinnings of the retro-cueing effects have also been investigated using neurophysiological methods (Kuo, Stokes, & Nobre, 2012; Wallis et al., 2015) and evident within neuroimaging studies (e.g., Gazzaley & Nobre, 2012; Lepsien, Griffin, Devlin, & Nobre, 2005; Nobre et al., 2004).

Notably, retro-cues have also been found to benefit the WM retrieval of healthy older adults, attenuating, but not removing age-related deficits. Gilchrist et al. (2016), presented young and older adults with memory arrays consisting of five coloured shapes. Next, they were provided with an informative retro-cue pertaining either to the colour or shape of the to-be-proved object, or with a neutral cue. They found that, although older individuals were less accurate compared to young participants, they also benefitted from the presence of the informative retro-cues (Gilchrist, Duarte, & Verhaeghen, 2016). Additionally, Mok et al. (2016) also showed that WM retrieval of older adults significantly benefitted from retro-cues. Investigating the source of errors, they also found that retro-cues conferred greater chances of recalling the target, lowered likelihood of guessing, and improved memory precision (Mok, Myers, Wallis, & Nobre, 2016). Whereas WM overall performance decreased with age, these studies show that retro-cues provide strong retrieval benefits across ageing.

Building on previous findings of both WM and LTM age-related retrieval degradation and considering the attenuating effect of WM retro-cues, leads to a question that remains unanswered. Do retro-cues also benefit LTM retrieval, and could older adults' decline also be reduced by this effect? Earlier retro-cueing findings represent a gateway towards numerous research questions that aim to uncover the relationship between and mechanisms underlying attention and memory of different timespans. At the same time, they also emphasise a gap in the literature that has not yet been addressed. Considering that WM and LTM may be

differentially affected by healthy ageing, it becomes important to learn whether retro-cues benefit both young and elderly adults' LTM retrieval abilities, or if the mechanism and relationship between the two systems changes with time.

In establishing hypotheses for these questions, a good starting point within the context of LTM research is the prominent Attention To Memory (AToM) theory which proposes that the internal orienting of attention during retrieval possibly mirrors the external deployment of attentional selection (Cabeza et al., 2008; Ciaramelli et al., 2008). Additionally, Duncan et al. (2012) suggested that the response of the hippocampal subfield CA1 as a match/mismatch detector was modulated depending on whether the relevant dimension was being attended to (Duncan et al., 2012). These results support the idea that in theory, selective attention can also modulate processes or activity underlying LTM retrieval. However, despite these theoretical accounts, there is no effective experimental approach that isolates attention orienting to contents in LTM.

For this reason, in this chapter I set out to investigate whether the benefits of retro-cueing extend to LTM processes, and if this could also represent a means to improve LTM memory retrieval performance in elderly individuals. Moreover, as the two memory systems are typically examined separately, using different measures, I also opened the line of research into whether young individuals' abilities to benefit from retro-cues correlates between the two memory systems, and whether this is preserved with ageing. Therefore, this study examines WM and LTM for the same material - spatial contextual associations - in younger and older adults and investigates the role that focusing attention may play in modulating performance in these two memory domains. For this, I developed two equivalent retro-cueing memory tasks that incorporated measures of both object identification and object-location binding in WM and LTM. I expected to find a decrease in retrieval abilities for both WM and LTM in older adults and a retro-cueing benefit for both age groups and memory systems. Additionally, I anticipated that I would find a correlation between benefits of retro-cueing in WM and LTM in both young adults and older adults.

2.2 Methods

2.2.1 Participants

This study was approved by the Central University Research Ethics Committee (CUREC) (research ethics project number: 08/H0606/133). All participants provided their informed consent prior to taking part in the study and were reimbursed for their time at a rate of £10/hour, as well as for their travel to the testing venue.

Thirty young participants (16 females, 14 males, age range 19-31, *M* = 25.1, *SD* = 5.6) were recruited from the community via local media and the Oxford Psychology Research (OPR) participant recruitment scheme (https://opr.sona-systems.com). Of these, two were excluded from the WM analysis because they were unable to perform the task above chance level (see Analysis section). The remaining twenty-eight participants were included in the WM analysis (13 females, 15 males, age range 19-31, *M* = 26.12, *SD* = 3.2). Six were excluded from the LTM analysis because they were unable to perform the task above chance level (see Analysis section). The remaining twenty-four participants were included both in the LTM and the comparisons between the two memory tasks (13 females, 11 males, age range 19-30, *M* = 24.25, *SD* = 2.4).

Thirty older participants (14 females, 16 males, ages range 62-81, *M* = 71.9, *SD* = 5.8) were recruited from the Friends of Oxford Dementia and Ageing Research platform (https://www.oxdare.ox.ac.uk/home). Two participants were excluded from the analysis, as they experienced nausea performing a virtual-reality task during the same session and they did not return to complete both sessions of the experiment. The remaining twenty-eight participants were included in the WM analysis (12 females, 16 males, ages range 62-80, *M* = 70.2, *SD* = 5.3). An additional seven participants were excluded from the LTM analysis because they were unable to perform the task above chance level (see Analysis section). The remaining twenty-one participants were included both in the LTM and the comparisons between the two memory tasks (10 female, 11 male, age range 63-79, *M* = 71.26, *SD* = 2.5).

All participants were fluent in English and had normal or corrected-to-normal vision and hearing. The two groups did not differ significantly in their number of years of education (see section 4.2.2 in the Results).

2.2.2 Experimental Setup

Participants completed the experiment in a group testing room in the Department of Experimental Psychology of the University of Oxford with a capacity of 20 people, although no more than 3 people were tested at one time. Participants each sat approximately 50 cm from the monitor (Dell U2312HM Monitor, 1920 x 1080 resolution; refresh rate 60 Hz). To respond to the task requirements, participants used the mouse and space bar on the keyboard. The mouse was used to identify target objects, whereas the space bar was used to indicate finding the target objects in a scene, or to indicate that a localisation response was made.

2.2.3 Protocol

Participants performed the study in two sessions, completed over successive days. Two experimental studies were completed over the two sessions, a navigation-based spatial memory study (Chapter 3) and a retro-cueing study. Only the retro-cueing study is discussed in this chapter. This contained two tasks, one that probed WM and the other that probed LTM. The order in which these two tasks were performed was counterbalanced across participants for the two testing days. Additionally, the order of the two studies was also counterbalanced across participants for each day.

On the first day, participants received instructions and were given a chance to familiarise themselves with the apparatus and to train on the tasks. They then completed the first experimental testing session for each study. In addition, participants completed an online set of questionnaires including demographic and descriptive questionnaires, and the Pittsburgh Sleep Quality Index. On the second day, participants completed the second

experimental session for each of the two studies. The order in which tasks were performed was counterbalanced across participants for both testing days.

For the study being considered in this Chapter, the first testing day started with an introduction from the researcher about the general purpose of the study and about the hardware participants were asked to use throughout the task. Next, participants performed a practice session to ensure they were comfortable using the mouse and keyboard to complete the task requirements. Following the practice session, participants completed the first experimental session of this study. Participants completed the second and final tasks during the second day of testing. Both tasks were programmed in Matlab R2018b (MathWorks).

2.2.4 Behavioural Stimuli

During the tasks, participants encoded and remembered the location of everyday objects within different scenes. A total of 192 photographic images of objects were randomly drawn from a set of 216 for each participant and for each of the two tasks of this study. There were two separate sets of objects for each task, to ensure that none of the objects appears in both tasks. Additionally, all object images were visually distinct from one another and easily identifiable. They were chosen from the following categories: toys, household items, food, clothing items, and sports equipment. These were selected from the Brain and Cognition Laboratory's in-house repository of stimuli curated by current and previous lab members. All objects were sized to fit within a 75 x 75 pixels box. Of the 192 objects in each task, 128 were associated with scenes, whereas 64 appeared as foils.

A total of 64 scenes were randomly selected from a pool of 96 for each task and each participant. These consisted of coloured photos of complex outdoor and indoor environments. The scenes were different between the two tasks. They were presented at a resolution of 1000 x 750 pixels surrounded by grey background.

Two objects appeared overlaid on each scene. All objects' locations were randomly generated within a set of constraints. Objects appeared an equal number of trials in each quadrant throughout the task. Within one trial, one object always appeared on the left half of the scene and the other on the right. Foils never appeared overlaid on any scene. All objects were at least 50 pixels away from the centre and the edges of the scene.

2.2.5 Behavioural Tasks

In this study, participants were asked to perform two tasks, one on each day of testing. These were used to quantify the effect of retro-cues on young and elderly participants' abilities to remember objects' identities and object-location associations at different timescales. One task measured retrieval in WM and the other in LTM.

2.2.5.1 WM Task

In the WM task, on each trial, participants encoded a memory array consisting of two everyday objects superimposed on a scene that appeared on the screen for 3000 ms. This was followed by either a predictive spatial retro-cue or an uninformative neutral cue. In the predictive retro-cue condition, one side of the diamond-shaped fixation marker briefly turned blue, indicating the location of the relevant item in the scene (left/right). In the uninformative neutral-cue condition, both sides of the diamond-shaped fixation turned blue and therefore provided no information. The cue was presented 1000 ms after the memory array had disappeared, lasted for 100 ms, and was followed by a 1000 ms delay period. Next, in the identification phase, participants were presented with a choice of two objects to the left and right of the fixation. One of the objects had previously appeared in the scene and the other was a novel object. Their location was randomised and had no consistent correspondence with encoded location of the objects. Participants were instructed to select the previously encoded items by clicking the left or right mouse button to indicate their choice. After selecting the remembered target object, the scene reappeared on the screen and participants had to move

the mouse cursor to the remembered location of the target object. They had to click the left mouse button to mark the location and press the space bar to complete the trial. These steps did not have a time limit. The task continued to the next trial once participants made a response. The inter-trial interval (ITI) was 1000 ms (Figure 2.1).

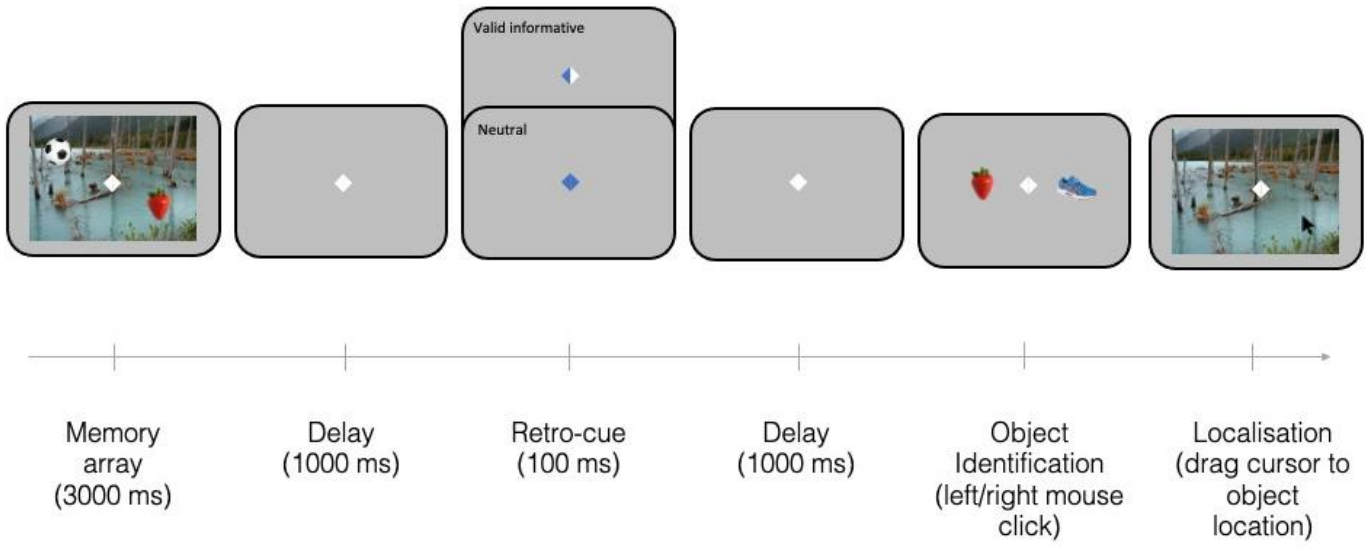

Figure 2.1 This schematic of the WM task design illustrates the timeline of one trial of the task. The objects are not illustrated to scale. Participants were first shown a memory array consisting of two everyday objects superimposed on a scene that appeared on the screen for 3000 ms. This was followed by either a valid informative retro-cue or a neutral cue (100 ms) that appeared 1000 ms after the offset of the memory array. Next, in the identification phase, participants were presented with a choice of two objects to the left and right of the fixation. One of the objects previously appeared in the scene and the other was a foil. After they selected the remembered target object, the scene reappeared on the screen and participants had to click on its remembered location.

Spatial retro-cues were 100% predictive (valid) and indicated the side (left/right) of the relevant item in the array that the participant would be probed about at the end of the trial. Neutral cues did not provide any spatial information about the item to be probed. Spatial and neutral retro-cues each made up 50% of the trials and appeared in a randomised order.

Participants performed one block of the task consisting of 32 valid retro-cued trials and 32 neutral cue trials randomly intermixed, yielding a total of 64 trials. Before beginning

the task, they also performed 6 practice trials using different stimuli from those of the task. They were instructed to respond as quickly and as accurately as possible.

The number of trials in this task was chosen based on previous studies that used similar paradigms to investigate the effect of retro-cues or to measure object-location binding abilities, as well as on the results of a pilot phase including three participants (Yoni Pertzov et al., 2015; Roüast, 2021; Souza & Oberauer, 2016). The number of trials used in similar reference studies was typically lower. However, considering the novel question regarding the relationship between WM and LTM introduced in this study, increasing the number of trails to 64 aimed to increase the reliability of the results.

2.2.5.2 LTM task

The LTM task consisted of an encoding phase and a retrieval phase, separated by a 20-minute break.

In the encoding phase, on each trial, participants were first shown two objects, one on each side of the central fixation marker, on a grey background (1000 ms). The memory array then appeared, which included the two objects embedded within a scene. Participants performed a visual search to find the two objects in a scene. They were asked to indicate when they had identified both objects by pressing the space bar on the keyboard, and then to locate each of the objects by using the mouse to click on their locations, in no specific order. They had a total of 6000 ms to respond. The next trial would begin after both objects' locations were clicked, or, if no response was made, after the 6000 ms elapsed. Participants learned a total of 64 object-scene associations. The encoding phase consisted of three blocks, each block repeating the same 64 arrays in a randomised order (Figure 2.2 A).

The retrieval phase started after a 20 min break. The LTM retrieval task resembled the WM task. In the beginning of the trial, participants were presented with the previously learned scenes for 100 ms, but *without* the superimposed objects. This scene served as context for retrieving one of the previously learned objects at the end of the trial. During the ensuing

delay, either a spatial or neutral retro-cue appeared after 250 ms after the scene offset. Participants were then presented with a choice between two objects after a 1000-ms delay: one object had been previously learned within this scene context and the other object was a novel foil. They appeared on the left and right of the fixation marker, at random. Participants had to select the previously learned object by clicking the corresponding left or right mouse button. After identifying the object associated with the scene, participants were asked to mark its remembered location in the scene by dragging the mouse cursor and clicking the left button to respond. Next, they pressed the space bar to continue to the next trial (Figure 2.2 B).

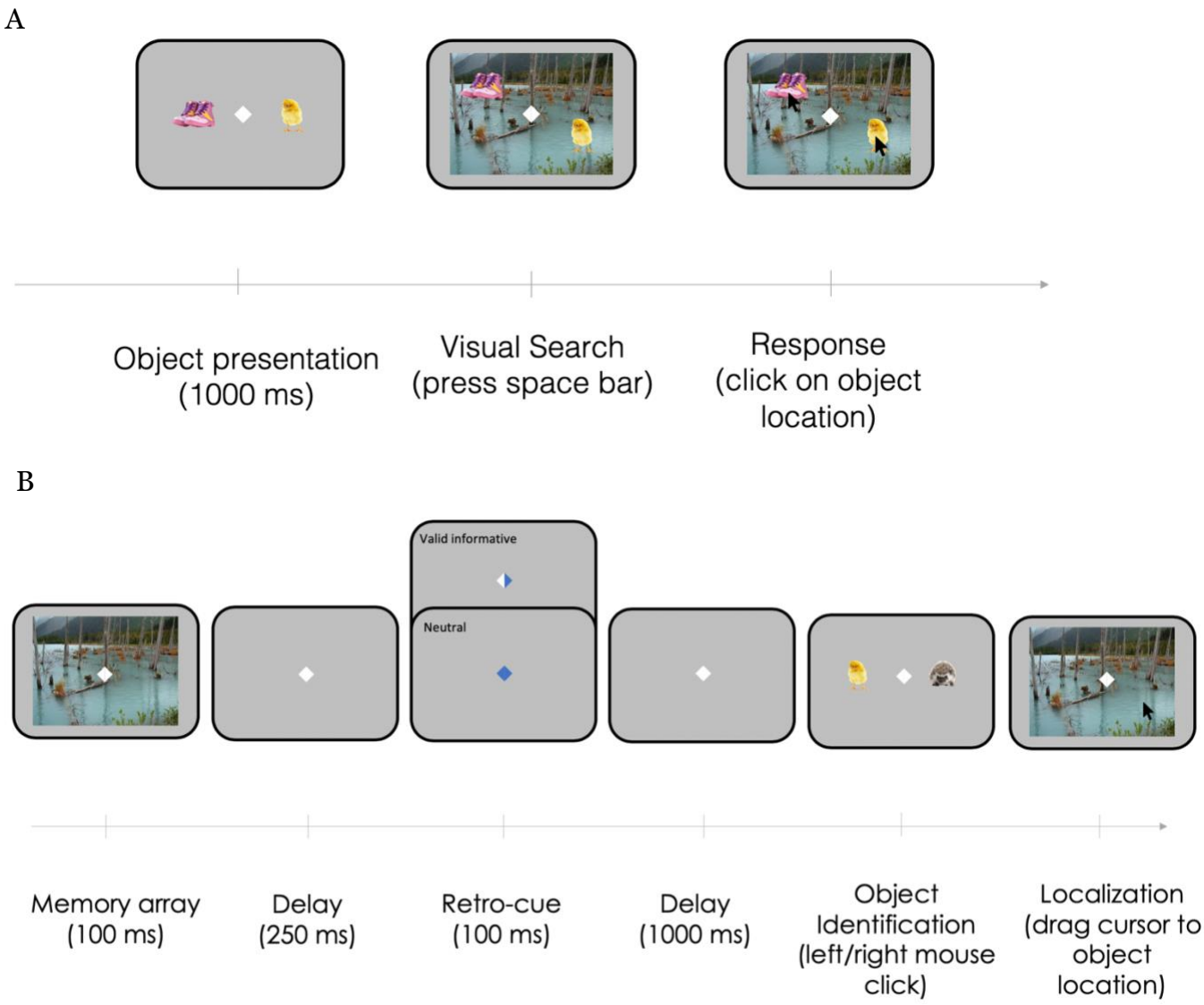

Figure 2.2 A. This schematic of the design of the encoding phase of the LTM task illustrates the timeline of one encoding trial. Participants were first shown two objects on each side of the fixation on a grey background (1000 ms). After 1000 ms, the memory array appeared and they were asked to perform a visual search, to find the two objects in a scene. They had to respond only once they identified both objects pressing the space bar on the keyboard, and then by clicking on the two objects consecutively to mark their locations, in no specific order. They had 6000 ms to respond. B. This schematic of the design of the retrieval phase of the LTM task illustrates the timeline of one trial of the task. Participants were first presented with the previously learned scenes for 100 ms without the superimposed objects. Either a valid informative retro-cue or a neutral cue appeared after 250 ms, followed by a choice between one of the objects previously associated with the respective scene and a foil. After they selected the remembered target object, the scene reappeared on the screen and participants had to click on its remembered location.

Participants performed one block of the retrieval phase, consisting of 32 valid retro-cued trials and 32 neutral cue trials in random order, being probed on previously encoded associations. Before each phase, they also performed 6 practice trials using different stimuli from those of the task. They were instructed to respond as fast and as accurately as possible.

The number of trials in this task was chosen based on a previous study that used a similar paradigm to investigate the effect of retro-cues on LTM retrieval in young participants, on studies that measured object-location association abilities, as well as on the results of a pilot phase including three participants (Yoni Pertzov et al., 2015; Roüast, 2021; Souza & Oberauer, 2016). Originally the task was piloted using 128, and then 96 trials. However, similar to previous pilots in the research group, it was found that participants could not hold that many associations in memory. For this reason, the number of trials was reduced to 64.

2.2.6 Analysis

The main aims of the analyses were to compare retrieval abilities of the two age groups at different timepoints and to determine whether and in what ways retro-cues modulate these abilities.

Data were pre-processed and analysed using R Studio version 3.4.2 (2017). Trials were excluded from the final analysis in both the WM and LTM tasks if identification response times were faster than 100 milliseconds, or longer than 3 standard deviations from individual means across conditions. These exclusion criteria aimed at eliminating trials where participants were either too slow in responding, denoting that they were likely distracted or not paying attention to the task, or unusually fast, responding faster than what would be necessary to think of the correct response for the specific trial (Roüast, 2021). In total, approximately one percent of trials were excluded. Additionally, only the trials in which target objects were accurately identified were included in the analysis of identification response times and localisation errors. Finally, participants were only included in the analysis if their object identification performance was above chance level overall (>50%). This criterion was applied following

analysis protocols previously established in the research group and was motivated by incidents where participants would not engage with the task and would perform randomly in order to receive compensation for their time (Roüast, 2021). Alternatively, accuracies below 50% could also indicate a lack of learning of the task stimuli. To avoid including these cases in the data analysis, these participants were excluded. This criterion was applied separately for the WM and LTM analyses, whereas participants who did not perform above chance level for both tasks were excluded from the comparisons between the two memory systems.

The dependent measures computed examined both the quality of participants' retrieved memories and the speed of access to these memories. Their accuracy in identifying the target objects and their response times in the identification part of the tasks, as well as their localisation errors when asked to place the target object in the associated scene were investigated. The localisation error was calculated as the Euclidean distance between the participant's response and the correct location of the target object.

Additionally, a three-parameter two-dimensional mixture model was fitted to the pre-processed localisation error data from accurate trials using the maximum likelihood estimation on MemToolbox2D (Grogan et al., 2020) and MATLAB release 2018b (the MathWorks Inc., Natick, MA, USA). The three parameters were memory precision, the proportion of guesses, and swap errors. When participants only remember the target location approximately this can lead to decreases in precision. When they remember the features encoded but not their associations, this could lead to swaps. Lastly, guesses are made when participants do not remember the required information and respond randomly. This model relies on the idea that absolute localisation error which provides an overview of performance can be deconstructed into measures of precision, guesses and swaps, breaking it down for a more detailed analysis. This model is similar to the one described by Bays, Catalao and Husain (Bays et al., 2009) but adapted for two-dimensional data (Grogan et al., 2020).

First, participants' performance was examined separately in the WM and the LTM tasks using 2 x 2 mixed-model ANOVAs for each of the dependent measures, with cue

condition as the within-subject factor and age group as the between-subject factor. Additionally, correlations between participants' performance during neutral trials and their retro-cueing benefits were investigated using Pearson correlations and compared between the two age groups using Fisher tests. What is more, for the LTM task, the relationship between participants' identification RTs during learning and their retro-cueing benefits was analysed using a Pearson correlation and compared between the two age groups using a Fisher test. Lastly, the relationship between retro-cueing benefits within the two memory systems was compared for each of the three dependent measures and each age groups using Pearson correlations. These relationships were also compared between the two age groups using Fisher tests. Prior to conducting these statistical tests, the assumption of homogeneity of variance was tested using Levene's test, whereas the normality of the distribution of the values was visualised using histograms, the values of skewness and kurtosis, and tested using the Shapiro-Wilk test. All assumptions were met.

2.3 Results

2.3.1 Working Memory

To assess the effects of ageing and retro-cues on participants' abilities to retrieve the target objects' identities and locations, identifications accuracies, response times and localisation errors were calculated averaging across all objects and scenes and compared between the two age groups and cue conditions. The results showed that the retro-cues benefitted participants' identification accuracies. Additionally, young individuals were faster and made smaller errors stemming from fewer guesses and swaps compared to elderly participants. They were also more precise in their location retrieval.

Identification accuracies were compared using a mixed-model ANOVA with age group as the between-subject factor and cue condition as the within-subject factor. This revealed a main effect of cue ($F(1,54) = 4.2$, $p = .04$, $\eta^2 = .01$) suggesting that all participants identified the target objects correctly more in retro-cued trials ($M = 0.92$, $SD = 0.09$) compared to

neutral trials (M = 0.90, SD = 0.10). On the other hand, the main effect of age was not significant ($F(1,54) = 2.54$, $p = .11$, $\eta^2 = .05$), indicating that young and old participants showed comparable identification accuracies. The interaction between age and cue condition was also not significant ($F(1,54) = 0.21$, $p = .65$, $\eta^2 = .001$) (Figure 2.3 A).

Next, identification response times were similarly compared using a mixed-model ANOVA with age group as the between-subject factor and cue condition as the within-subject factor. The significant effect of age group ($F(1,54) = 44.59$, $p < .001$, $\eta^2 = .5$) revealed that young participants (M = 752.3, SD = 293.1) identified the target objects faster compared to elderly individuals (M = 1507.2, SD = 461.5), whereas the significant main effect of cue condition ($F(1,54) = 17.08$, $p < .001$, $\eta^2 = .03$), suggested that all participants respond faster on retro-cued trials (M = 1027.2, SD = 510.7) compared to neutral trials (M = 1163.7, SD = 553). The interaction between age and cue condition was not significant ($F(1,54) = 0.79$, p = .38, $\eta^2 = .002$) (Figure 2.3 B).

The localisation error was also compared using a mixed-model ANOVA with age group as the between-subject factor and cue condition as the within-subject factor. This revealed a significant main effect of age group ($F(1,54) = 39.57$, $p < .001$, $\eta^2 = .4$), showing that young participants (M = 65.2, SD = 39.3) made smaller errors compared to elderly individuals (M = 138.2, SD = 45.8) when retrieving the location of the target objects. Neither the main effect of cue condition ($F(1,54) = 1.5$, $p = .22$, $\eta^2 = .009$) nor the interaction between age and cue condition ($F(1,54) = 0.58$, $p = .45$, $\eta^2 = .004$) were significant (Figure 2.3 C).

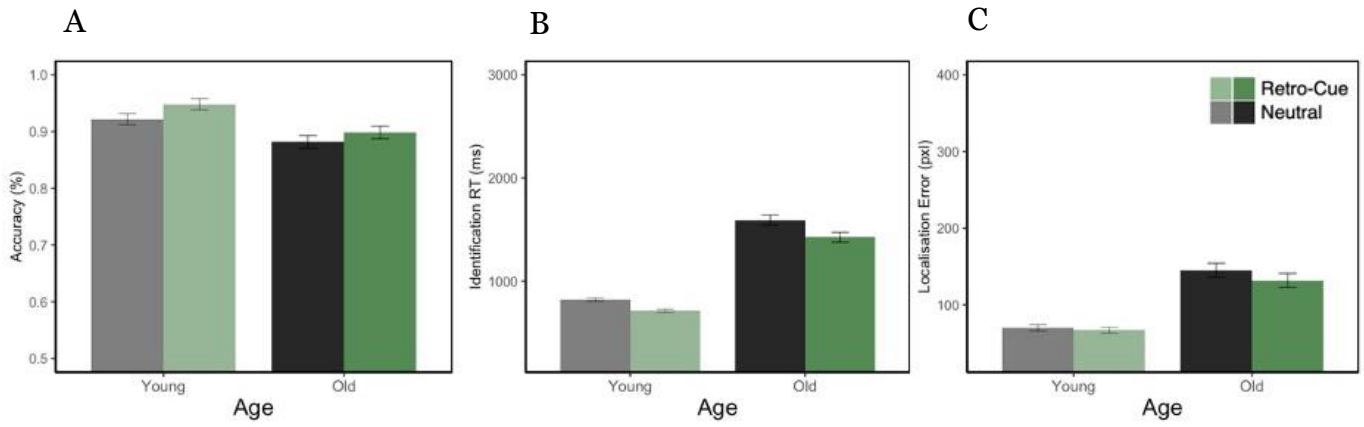

Figure 2.3 A. Average identification accuracy for the two age groups (young, old) and the two cue conditions (neutral, retro-cue). The error bars represent the standard error of the mean. Both age groups showed higher accuracies during retro-cued trials compared to neutral trials. B. Average identification response time for the two age groups and the two cue conditions. Young participants were faster compared to elderly individuals. Additionally, both groups responded faster on retro-cued trails compared to neutral trials. C. Average localisation errors for the two age groups and the two cue conditions. Younger participants made smaller errors compared to older participants.

Additionally, the source of localisation errors was investigated using a two-dimensional mixture model that revealed the proportions of swaps and guesses, as well as participants' precision. Mixed-model ANOVAs were used to draw comparisons between the two age groups and cue conditions. First, this revealed that elderly participants (M = 0.07, SD = 0.07) made significantly more guesses compared to young participants (M = 0.03, SD = 0.08) (F(1,54) = 4.7, p = .03, η^2 = .05). However, there was no difference in participants' proportions of guessing between neutral and retro-cued trials (F(1,54) = 0.47, p = .49, η^2 = .006), and age and cue condition did not interact significantly (F(1,54) = 0.2, p = .91, η^2 = .001) (Figure 2.4 A).

Next, elderly participants (M = 0.07, SD = 0.07) also swapped the locations of the objects in the scene more than young individuals (M = 0.01, SD = 0.04) (F(1,54) = 22.12, p < .001, η^2 = .2). The retro-cue did not benefit participants' swap rates significantly (F(1,54) =

0.64, p = .42, η^2 = .007), and age and cue condition did not interact significantly (F(1,54) = 0.32, p = .57, η^2 = .004) (Figure 2.4 B).

Lastly, old participants (M = 65.9, SD = 14.6) were more precise in their responses compared to young participants (M = 43.4, SD = 15.5) (F(1,54) = 29.12, p < .001, η^2 = .3). The retro-cues also did not benefit participants' precision significantly (F(1,54) = 0.19, p = .66, η^2 = .002) and the interaction between age and cue condition was not significant (F(1,54) = 0.15, p = .7, η^2 = .001) (Figure 2.4 C).

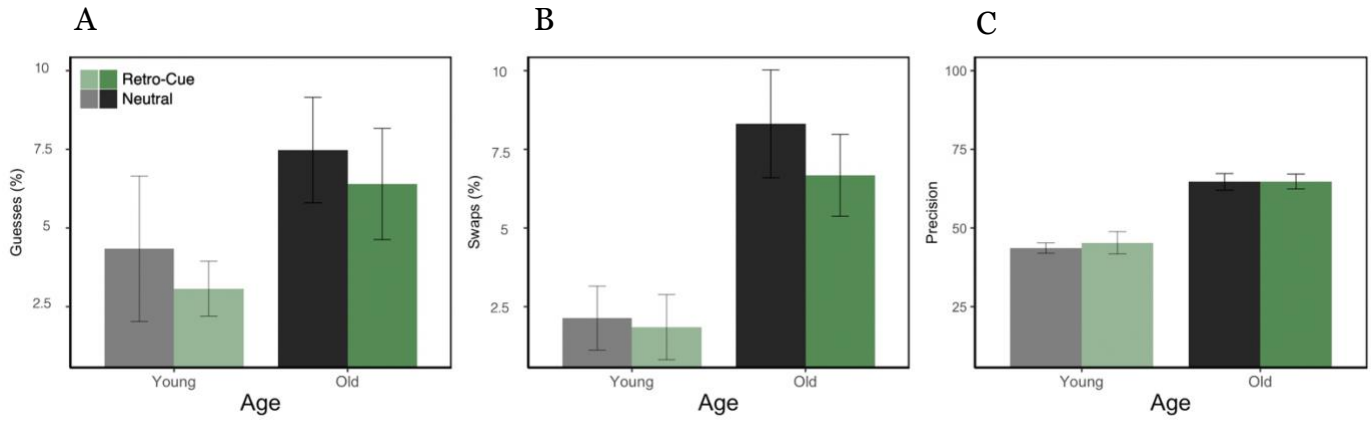

Figure 2.4 A. Average proportions of guesses for the two age groups (young, old) and the two cue conditions (neutral, retro-cue). Young made significantly fewer guesses compared to elderly individuals. The error bars represent the standard error of the mean B. Average proportions of swaps for the two age groups and the two cue conditions. Young made significantly fewer swaps compared to elderly individuals. C. Average localisation precisions for the two age groups and the two cue conditions. Old were significantly more precise in their object localisations compared to young individuals.

The relationship between participants' abilities to use retro-cues to benefit their WM performance and their performance on neutral trials was also assessed using Pearson correlations for identification accuracy, response time and localisation errors, separately for the two age groups. Retro-cue benefits were calculated as the % change between the two cue conditions for each variable. For identification accuracy, to calculate retro-cue benefits,

participants' performance during neutral trials was subtracted from their accuracies during retro-cued trials and the benefit was calculated as the percentage this difference represented from their neutral trials accuracies. Similarly, for identification response times, participants' performance during retro-cued trials were subtracted from their performance on neutral trials and the proportion this difference represented out of the neutral trials response time was considered to be the benefit of the retro-cues. Lastly, localisation error benefits were calculated as the percentage the difference between neutral trials and retro-cued trials represented out of their neutral trials performance. Therefore, the larger the numbers on the Y axes of Figure 2.5, the greater the retro-cueing benefit.

The results revealed a moderate negative correlation between young participants' identification accuracies during neutral trials and their retro-cue benefits on the same measure ($r(27) = -.6$, $p = .001$). This suggests that young individuals who had high identification accuracies on neutral trials had smaller retro-cue benefits. Old participants did not show a significant correlation ($r(27) = -.4$, $p = .07$). When comparing the relationship between the two age groups' correlations, the Fisher test revealed a non-significant difference ($p = .2$). Next, neither young ($r(27) = .3$, $p = .1$), nor old ($r(27) = .1$, $p = .4$) participants showed a significant correlation between their identification response time during neutral trials and their retro-cue benefits. Lastly, old ($r(27) = .7$, $p = .001$), but not young participants ($r(27) = .3$, $p = .07$) showed a strong positive correlation between their localisation errors during neutral trials and their retro-cue benefits for the same measure. This suggests that elderly participants who could accurately recall target locations during neutral trials improved their localisation more during retro-cued trials. When comparing the relationship between the two age groups' correlations, the Fisher test revealed a non-significant difference ($p = .09$) (Figure 2.5).

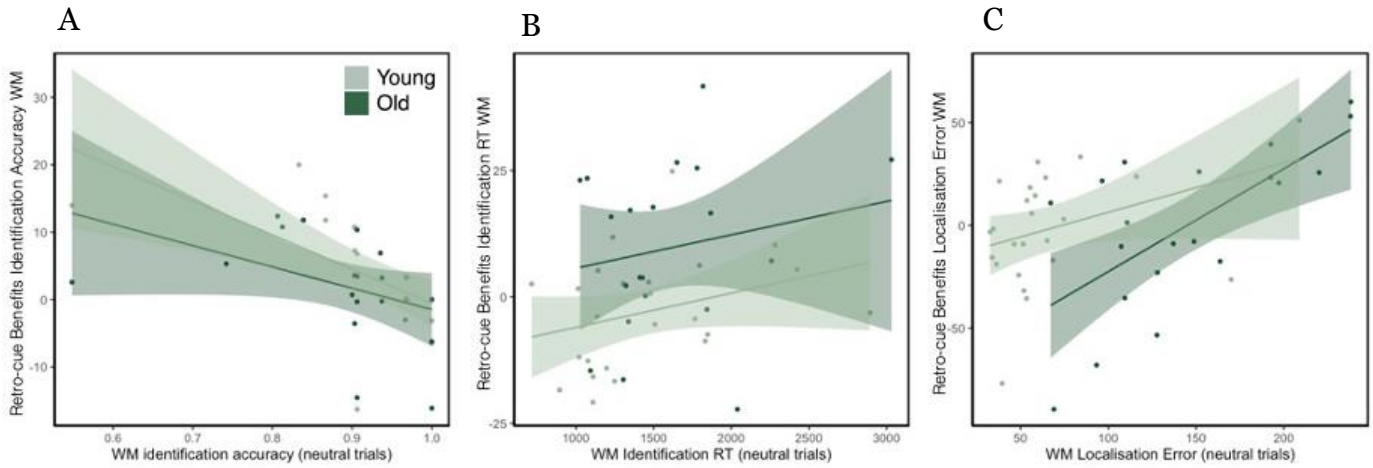

Figure 2.5 A. The plot illustrates correlations between participants' retro-cueing benefits and their performance during neutral trials for identification accuracy for both age groups. Young individuals who had high identification accuracies on neutral trials had smaller retro-cue benefits B. The plot illustrates correlations between participants' retro-cueing benefits and their performance during neutral trials for identification response time for both age groups. C. The plot illustrates correlations between participants' retro-cueing benefits and their performance during neutral trials for localisation error for both age groups. Elderly participants who could accurately recall target locations during neutral trials improved their localisation more during retro-cued trials.

2.3.2 Long-Term Memory

2.3.2.1 Learning

Participant's learning abilities were measured using identification response times during the initial visual-search phase of the task. They were compared between the age groups and the three blocks of learning. The results revealed that young participants identified the objects faster than elderly, although both age groups became faster with time.

To assess participants' learning during search blocks, a mixed-model ANOVA with age as the between-subject factor and block as the within-subject factor was used to examine identification response times. This revealed a significant main effect of age ($F(1,43) = 31.76$, $p < .001$, $\eta^2 = .37$), suggesting that young participants ($M = 835.8$, $SD = 471.2$) found the two objects faster than elderly participants ($M = 1648$, $SD = 658.4$). The main effect of block was also significant ($F(2,43) = 17.91$, $p < .001$, $\eta^2 = .09$) indicating that both groups respond faster

with every block. Lastly, age and block also interacted significantly ($F(2,43) = 4$, $p = .04$, $\eta^2 = .02$). This was further investigated first using two one-way ANOVAs, one for each age group. These revealed that whereas elderly participants improved significantly across the three blocks ($F(2,19) = 13.03$, $p < .001$, $\eta^2 = .14$) (Block 1: $M = 1992.1$, $SD = 723$; Block 2: $M = 1536.8$, $SD = 516.3$; Block 3: $M = 1415.1$, $SD = 601.7$), young participants remained relatively consistent (Block 1: $M = 955.5$, $SD = 388.1$; Block 2: $M = 815.4$, $SD = 446.7$; Block 3: $M = 732.3$, $SD = 559.5$) ($F(2,22) = 4.08$, $p = .047$, $\eta^2 = .03$). Additionally, the slopes between the first and second block and between that second and third block were calculated and compared between groups using independent samples t-tests. The pattern showed that the greatest improvement for old participants occurred between the first two blocks, where their performance improved more compared to young individuals ($t(43) = 2.49$, $p = .01$, $d = .7$), whereas the improvement from the second to the third block ($t(43) = 0.64$, $p = .52$, $d = .2$) was comparable between the two groups (Figure 2.6).

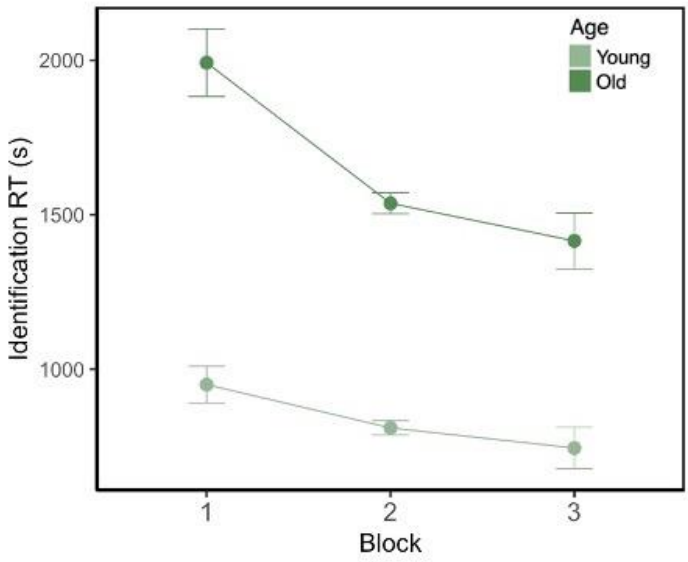

Figure 2.6 Average identification response times during each search block for elderly and young participants. Young participants found the two objects faster compared to elderly individuals. Additionally, old participants improved their performance across the three blocks, whereas young participants remained relatively consistent. The error bars represent the standard error of the mean.

2.3.2.1 Retrieval

Participants' retrieval performance was investigated next using identification accuracies, response times and localisation errors averaged across all objects and environments and compared between the two age groups and cue conditions. The results showed that young participants were overall faster at identifying the target objects compared to elderly individuals. Additionally, young participants made smaller localisation errors compared to older adults. Both groups performed better during retro-cued trials, although young participants benefitted more from retro-cues.

A mixed-model ANOVA with age as the between-subject factor and cue condition as the within-subject factor was first used to compare mean identification accuracies. This revealed no significant differences between the two groups (Young: (M = 0.80, SD = 0.13; Old: M = 0.75, SD = 0.10) (F(1,43) = 1.87, p = .17, η^2 = .03) or cue conditions (Retro-cue: M = 0.79, SD = 0.12; Neutral: M = 0.78, SD = 0.12) (F(1,43) = 0.08, p = .78, η^2 = .001). The interaction between age and cue condition was also not significant (F(1,43) = 0.55, p = .46, η^2 = .003) (Figure 2.7 A).

Next, a similar mixed-model ANOVA was used to investigate identification response times. This revealed a main effect of age (F(1,43) = 11.54, p < .001, η^2 = .28), with young participants (M = 1476, SD = 504.8) responding faster compared to elderly ones (M = 2341.5, SD = 870.3). There was no significant difference between the two cue conditions (F(1,43) = 1.22, p = .27, η^2 = .003) and no significant interaction between age and cue condition (F(1,43) = 2.16, p = .14, η^2 = .005) (Figure 2.7 B).

A similar analysis of participants' localisation errors revealed a main effect of age (F(1,43) = 5.83, p = .02, η^2 = .1), with young participants (M = 241.1, SD = 83.1) making smaller errors compared to older ones (M = 286.7, SD = 57.6), as well as a significant main effect of cue (F(1,43) = 23.63, p < .001, η^2 = .09), revealing better performance for both groups on retro-cued trials (M = 239.2, SD = 79.5) compared to neutral trials (M = 284.4, SD = 65.2).

The interaction between age and cue was also significant ($F(1,43) = 5.73$, $p = .02$, $\eta^2 = .02$). This was further investigated by comparing the benefits of retro-cues between the two groups using an independent sample t-test. These were calculated as the % change in localisation errors from neutral trials to retro-cued trials. This revealed that retro-cues benefitted young participants ($M = 22.5$, $SD = 24.1$) significantly more than elderly participants ($M = 7.4$, $SD = 17.2$) ($t(43) = 2.4$, $p = .02$, $d = .7$) (Figure 2.7 C).

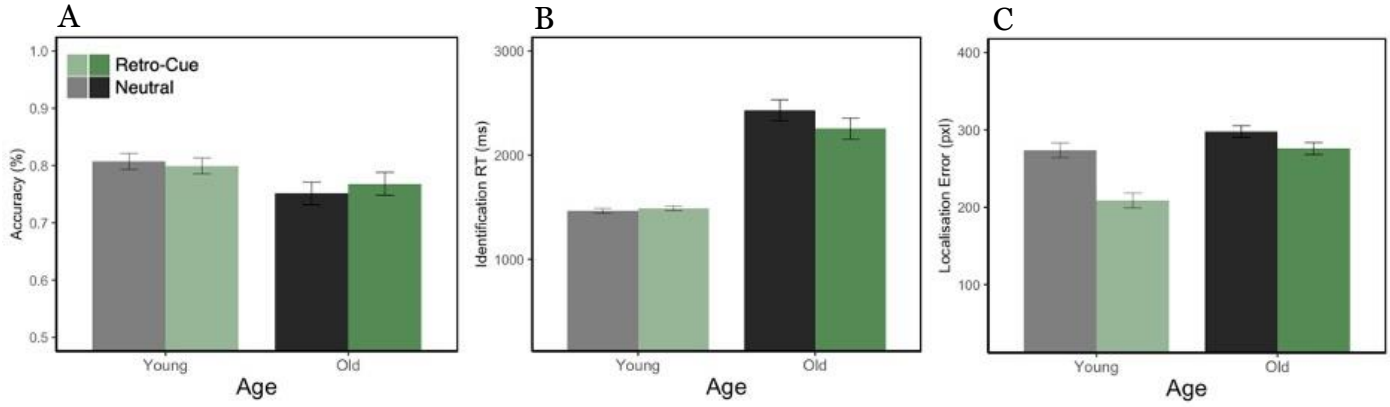

Figure 2.7 A. Average identification accuracy for the two age groups and the two cue conditions. The error bars represent the standard error of the mean B. Average identification response time for the two age groups and the two cue conditions. Young participants were faster compared to elderly individuals. C. Average localisation errors for the two age groups and the two cue conditions. Younger participants made smaller errors compared to older participants. Additionally, both groups performed better on retro-cued trials compared to neutral trials, with young participants benefitting more from retro-cues compared to old participants.

The source of localisation errors was also investigated using a two-dimensional mixture model that revealed the proportions of swaps and guesses, as well as participants' precision. Mixed-model ANOVAs were used to draw comparisons between the two age groups and cue conditions.

First, this revealed that participants made significantly more guesses during neutral ($M = 0.5$, $SD = 0.2$) trials compared to retro-cued trials ($M = 0.4$, $SD = 0.2$) ($F(1,43) = 19.26$, $p < .001$, $\eta^2 = .1$). What is more, age and cue condition interacted significantly ($F(1,43) = 5.8$,

p = .02, η^2 = .03). However, there was no difference between the two groups' proportions of guessing (F(1,43) = 2.97, p = .09, η^2 = .05). The interaction was further investigated by comparing the benefits of retro-cues on the proportion of guesses of the two groups using an independent sample t-test. These were calculated as the % change in the proportion of guessing from neutral trials to retro-cued trials. This revealed that retro-cues benefitted young participants (M = 42.3, SD = *22.1*) significantly more than elderly participants (M = 9.22, SD = *36.1*) (t(43) = 2.8, p = .01, d = .7) (Figure 2.8 A).

Next, the ANOVA results also revealed that elderly participants (M = 0.05, SD = *0.07*) swapped the locations of the objects more than young individuals (M = 0.02, SD = *0.03*) (F(1,43) = 8.75, p = .005, η^2 = .08). The retro-cue did not benefit participants' swap rates significantly (F(1,43) = 0.09, p = .76, η^2 = .001), and age and cue condition did not interact significantly (F(1,43) = 0.98, p = .32, η^2 = .01) (Figure 2.8 B).

Lastly, the ANOVA results for precision showed a main effect of cue condition (F(1,43) = 4.77, p = .035, η^2 = .05). This effect was further investigated by comparing the performance between retro-cued and neutral trials within each age group using paired-sample t-tests. This revealed that retro-cues benefitted young participants' precision significantly (t(22) = 1.8, p = .01, d = .7), but not older participants' (t(19) = 0.3, p = .09, d = .3).

The two age groups did not differ significantly in their precision (F(1,43) = 0.05, p = .83, η^2 = .001) and the interaction between age and cue condition was not significant (F(1,43) = 1.64, p = .2, η^2 = .02) (Figure 2.8 C).

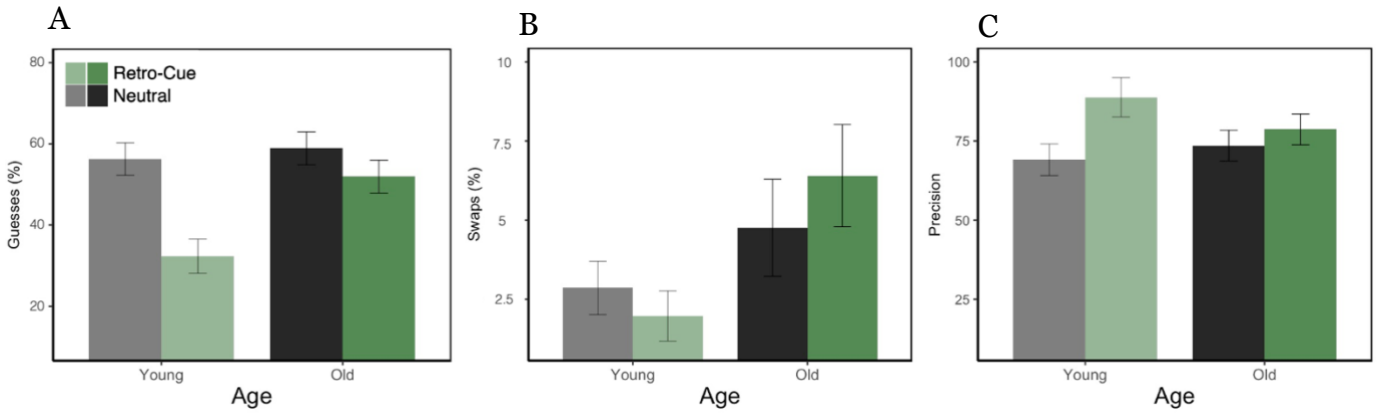

Figure 2.8 A. Average proportions of guesses for the two age groups and the two cue conditions. Participants made fewer guesses on retro-cued trails compared to neutral trials, with young participants benefitting from retro-cues more than elderly participants. The error bars represent the standard error of the mean B. Average proportions of swaps for the two age groups and the two cue conditions. Young made significantly fewer swaps compared to elderly individuals. C. Average localisation precisions for the two age groups and the two cue conditions. All participants were more precise in their localisation during retro-cued trials compared to neutral trials.

The relationship between participants' abilities to use retro-cues to benefit their performance and their LTM learning identification response time was also assessed using Pearson correlations for retrieval identification accuracy, response time and localisation errors. Retro-cue benefits were calculated as the % change between the two cue conditions.

The results revealed that the level of learning did not correlate with young ($r(22) = .1$, $p = .5$) or old ($r(19) = -.03$, $p = .9$) participants' retro-cue benefits on retrieval identification accuracy. Next, neither young ($r(22) = -0.2$, $p = .2$), nor old ($r(19) = .2$, $p = .2$) participants showed a significant correlation between their identification response time during learning and their retro-cue benefits on retrieval response times. Lastly, neither young ($r(22) = -.1$, $p = .6$) nor old participants ($r(19) = .2$, $p = .2$) showed a significant correlation between their learning and their retro-cue benefits on localisation errors (Figure 2.9).

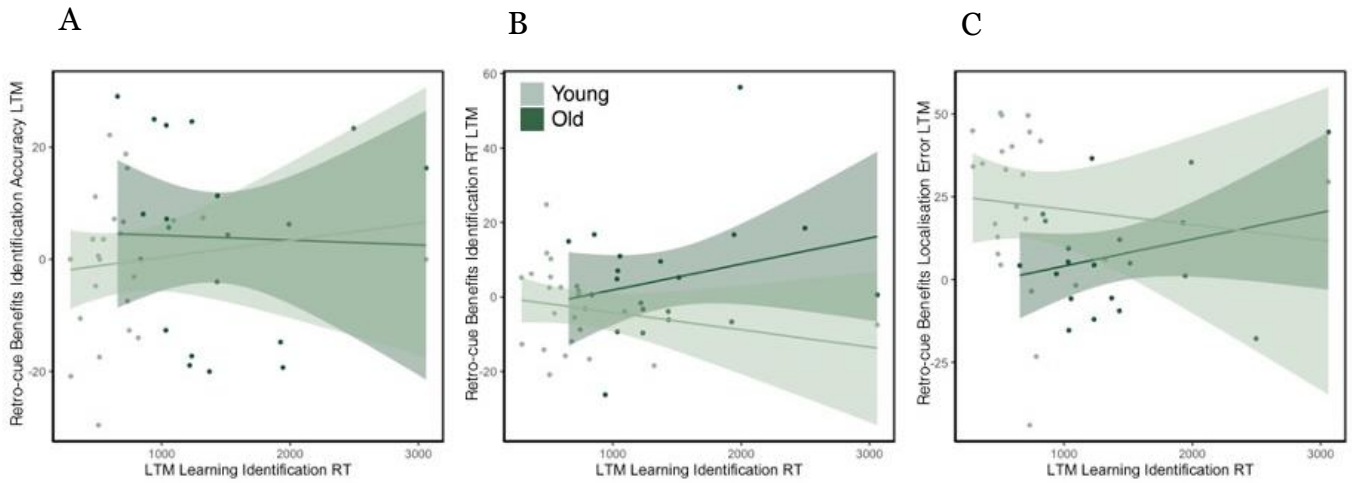

Figure 2.9 A. The plot illustrates correlations between participants' retro-cueing benefits on identification accuracy and their learning identification response times for both age groups. B. The plot illustrates correlations between participants' retro-cueing benefits on identification response times and their learning identification response times for both age groups. C. The plot illustrates correlations between participants' retro-cueing benefits on localisation errors and their learning identification response times for both age groups.

The relationship between participants' abilities to use retro-cues to benefit their performance and their results on neutral trials in LTM was also assessed using Pearson correlations for identification accuracy, response time and localisation errors. The results revealed that a strong negative correlation between old participants' identification accuracies during neutral trials and their retro-cue benefits on the same measure ($r(19) = -.7$, $p < .001$). This suggests that old individuals who had low identification accuracies on neutral trials showed smaller retro-cue benefits. Young participants did not show a significant correlation ($r(22) = -0.2$, $p = .2$). When comparing the relationship between the two age groups' correlations, the Fisher test revealed a significant difference ($p = .03$), indicating the possibility of different patterns of retro-cue modulation with ageing. Next, neither young ($r(22) = 0.3$, $p = .1$) nor old ($r(19) = 0.4$, $p = .07$) participants showed a significant correlation between their identification response time during neutral trials and their retro-cue benefits. Lastly, neither young ($r(22) = 0.1$, $p = .4$) nor old ($r(19) = -0.02$, $p = .9$) participants showed

a significant correlation between their identification response time during neutral trials and their retro-cue benefits (Figure 2.10).

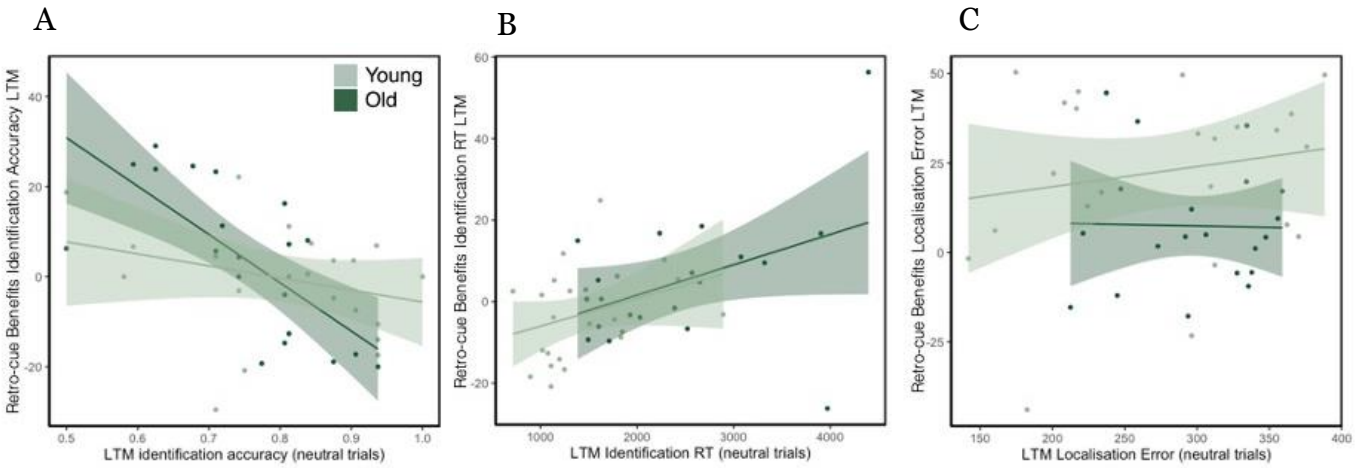

Figure 2.10 A. The plot illustrates correlations between participants' retro-cueing benefits and their performance during neutral trials for identification accuracy for both age groups. Old individuals who had high identification accuracies on neutral trials also showed smaller retro-cue benefits. The relationships differed between the two age groups indicating towards the possibility of different patterns of retro-cue modulation with ageing. B. The plot illustrates correlations between participants' retro-cueing benefits and their performance during neutral trials for identification response time for both age groups. C. The plot illustrates correlations between participants' retro-cueing benefits and their performance during neutral trials for localisation error for both age groups.

2.3.3 Relationship Between the Two Memory Systems

The relationships between participants' performance in WM and LTM were first investigated. For this purpose, a series of Pearson correlation tests for identification accuracy, identification response time, and localisation errors in neutral trials were conducted.

First, the correlation between identification accuracies during WM and LTM was measured. This revealed that the two performances were not correlated for either young participants ($r(22) = .2$, $p = .3$) or for elderly participants ($r(19) = -.2$, $p = .3$). (Figure 2.11 A). When looking at the relationship between WM identification response times and those measured in LTM, moderate positive correlations were observed both for young ($r(22) = .5$, $p = .008$) and elderly participants ($r(19) = .4$, $p = .03$). Participants who were quick to identify

target objects in WM were also quick to identify targets in LTM (Figure 2.11 B). When comparing the relationship between the two memory systems between the two age groups, the Fisher test revealed that it did not differ according to age (p = .4). Lastly, neither young participants' ($r(22) = .3$, $p < .13$) nor older participants' ($r(19) = .1$, $p = .4$) localisation errors correlated across the two tasks (Figure 2.11 C).

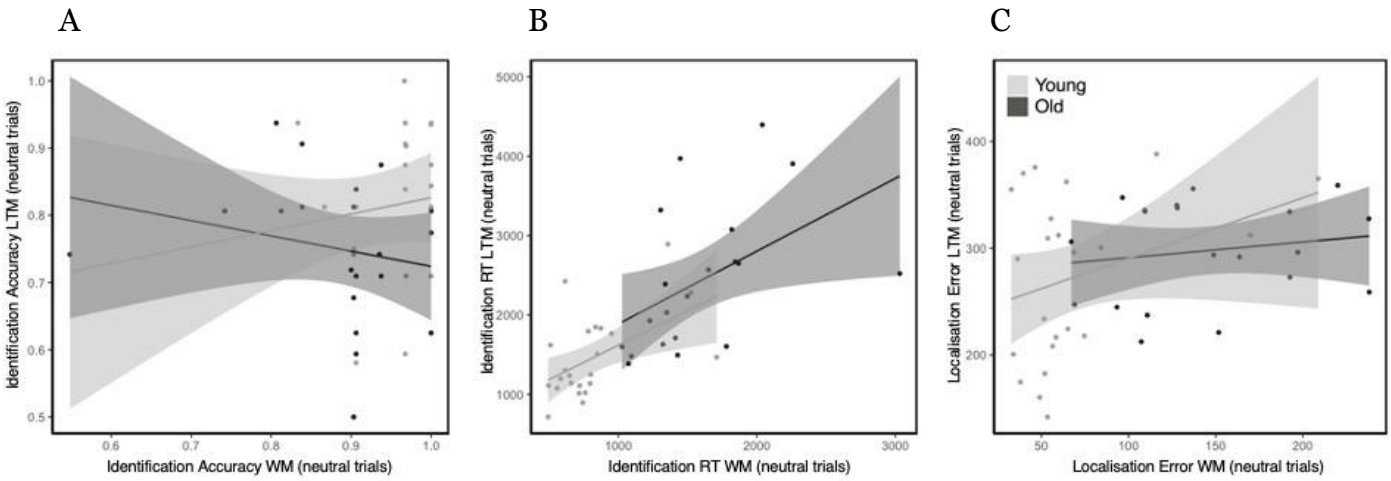

Figure 2.11 A. The plot illustrates correlations between participants' identification accuracy in WM and LTM for both age groups in neutral cue trials. B. The plot illustrates correlations between participants' identification response times in WM and LTM for both age groups in neutral cue trials. Participants who were quick to identify target objects in WM were also quick to identify targets in LTM. C. The plot illustrates correlations between participants' localisation errors in WM and LTM for both age groups in neutral cue trials.

To examine whether participants' abilities to use retro-cues in the WM task correlated with their ability to do the same in the LTM task, a measure of benefit was calculated as the % change in performance from neutral to retro-cued trials on all three dependent measures. Significant relationships between these benefits were then examined using Pearson correlations and compared between age groups using Fisher tests.

The tests revealed that retro-cueing benefits on identification accuracy in the two memory tasks did not correlate significantly for young (r(22) = .05, p = .7) or elderly

participants (r(19) = -.35, p = .1). Similarly, benefits on identification response times did not correlate between the two memory systems for young (r(22) = -.2, p = .3) or for elderly participants (r(19) = -.24, p = .2). Lastly, retro-cueing benefits correlated between the two memory systems for localisation errors of young participants (r(22) = .57, p = .003), suggesting that participants who could use retro-cues to improve their performance in WM, could also benefit from retro-cues in LTM. The same correlation was not significant for elderly participants (r(19) = .16, p = .65). Comparing the two relationships between the two age groups revealed a significant difference (p=0.04), suggesting different possible patters of use (Figure 2.12).

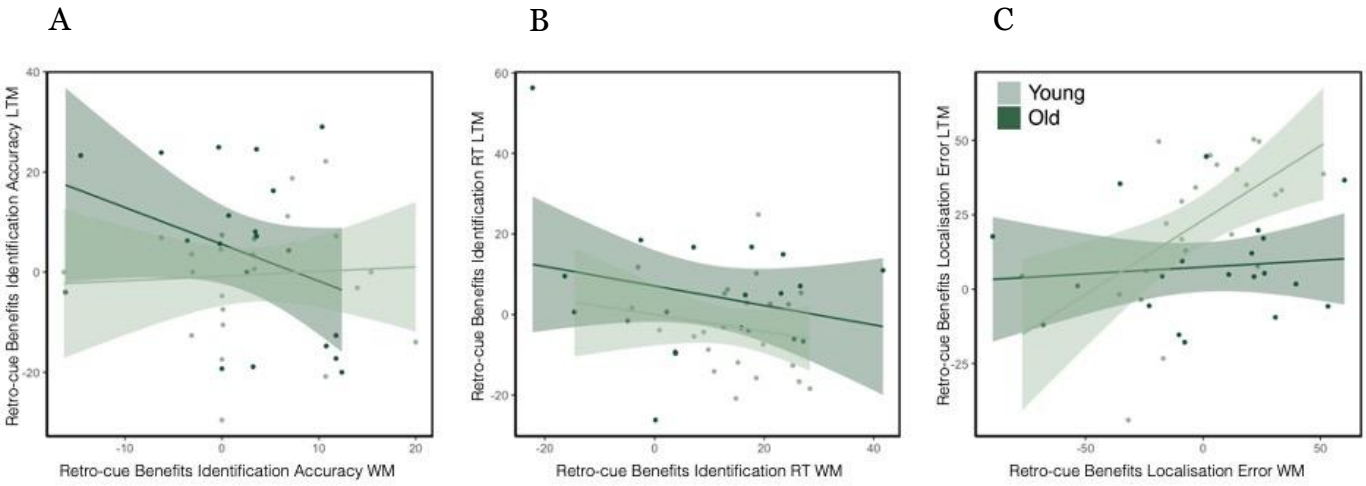

Figure 2.12 A. The plot illustrates correlations between participants' retro-cueing benefits for identification accuracy for both age groups. B. The plot illustrates correlations between participants' retro-cueing benefits for identification response times for both age groups. C. The plot illustrates correlations between participants' retro-cueing benefits for localisation errors for both age groups. The plot reveals that young participants who successfully used retro-cues in the WM task also benefitted from retro-cues in the LTM task.

2.4 Discussion

The current study used two novel continuous report tasks to investigate the retro-cueing effects on WM and LTM performance in both young and elderly individuals in a sensitive and comparable way. Equivalent probing of retrieval in the two tasks enabled us to measure and compare baseline retrieval abilities and retro-cueing effects both on access to

memories and on the quality of the representations in the two memory systems. Additionally, a model-based analysis was used to explore whether retro-cue benefits stem from either a decreased probability of guessing or swaps or an increase in the precision of representations. It was expected that older adults would show declined retrieval abilities WM and LTM compared to young participants and that both age groups would benefit from retro-cueing in the two memory tasks. Additionally, I anticipated that I would find a correlation between benefits of retro-cueing in WM and LTM for both young and older adults.

First, during neutral trials of the WM task, young adults were faster at identifying the target objects and made smaller localisation errors compared to elderly individuals. Additionally, the worse localisation performance of elderly adults stemmed from swapping the locations of the target and non-target objects, and from a decrease in response precision. These findings are consistent with previous reports of age-related WM impairments of objects' locations retrieval (Lugtmeijer et al., 2019; Pertzov et al., 2015). Similarly, age differences were observed across all measures when analysing both neutral and retro-cued trials of the WM task. This suggests that despite any benefit of orienting attention internally, the age-related deficit remains consistent.

On the other hand, during the neutral trials of the LTM task young and elderly adults only differ in their response times to identify target objects. Previous studies found age-related memory decline in both accuracy and localisation precision measures (Korkki et al., 2020; Salvato et al., 2016a). The current findings could stem from a lack of statistical power, rather than from a lack of differences between the two groups. When analysing all trials of the LTM task, age differences were observed for identification response time, localisation error, as well as sources of errors with elderly participants mis-binding the locations of the two objects of a scene more compared to young adults. These results align with earlier studies that also emphasise an age-related decrease in LTM performance (Chalfonte & Johnson, 1996; Kessels et al., 2007; Lugtmeijer et al., 2019; Naveh-Benjamin et al., 2003; Salvato et al., 2016).

Additionally, the age-related swap differences identified both in the WM and the LTM add to the evidence supporting the associative deficit theory of memory decline with ageing (Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2004). These findings indicate that, indeed, older adults exhibit a disproportionate decline in memory for bound, associative information, relative to memory for individual objects (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000).

Next, retro-cueing effects on young and elderly participants' WM retrieval performance were investigated. In line with previous research focused on young participants (Griffin & Nobre, 2003; Lepsien et al., 2005b; Souza & Oberauer, 2016; Souza et al., 2016), healthy older adults were also able to use retro-cues to benefit their WM retrieval. Similarly, to previous results from studies of young adults, retro-cues improved participants' access to the target information. However, there were no observed benefits in the quality of memory retrieval. Although several studies have previously tested the effectiveness of retro-cues in elderly participants the results remain mixed (Duarte et al., 2013; Mok et al., 2016a; Newsome et al., 2015). Duarte et al. (2013) and Newsome et al. (2015) showed that older adults were unable to benefit from retro-cues using a colour change-detection task. However, an error on binary choice of items does not imply no memory of an item at all. Similarly, a correct choice does not reflect the resolution of the respective memory (Ma et al., 2014). Gilchrist and colleagues found that, in fact elderly participants were able to equally benefit from retro-cues compared to young individuals (Gilchrist et al., 2016). However, in their experiment they used verbal cues pertaining to either the colour or the shape of the encoded objects, and the task also demanded binary responses (Gilchrist et al., 2016). On the other hand, both Mok et al. (2016) and the current study used spatial cues and precision measures that may be more sensitive to subtle behavioural differences between cue conditions (Mok et al., 2016a; Zokaei et al., 2015).

Prior studies supporting the resource deficit theory stating elderly individuals have a reduced ability to inhibit irrelevant stimulation leading to decreased retrieval performance

found that older adults are impaired in the ability to suppress irrelevant items from entering WM, which may contradict current results (Gazzaley et al., 2008, 2005; Hasher & Zacks, 1988; Zanto, Toy, & Gazzaley, 2010). However, these studies investigated participants' ability to suppress irrelevant items at encoding, whereas this study tested for the effect of selective attention after encoding. What the current results suggest is that retro-cues may also help to compensate for elderly adults' declining abilities to suppress irrelevant information, by reducing cognitive load and marking the to-be-cued information for faster access (Souza & Oberauer, 2016). To test this explicitly, future work may consider including distracting events during the delay period as well as retro-cues.

What is more, this is the first study to identify a mediating effect of selective attention for improved WM retrieval for old adults using complex stimuli, such as real-life everyday objects and scenes, compared, for example, to oriented coloured bars. This is valuable as it demonstrates that the benefits of retro-cueing remain even when complexity and task demand increase, in contexts with higher ecological validity.

Whether participants' memory retrieval performance during neutral trials correlated with their abilities to use the retro-cues to improve was also addressed. Negative correlations for young adults' identification accuracy in WM and old adults' identification accuracy in LTM indicated that those who retrieved most target objects, benefitted the least from retro-cues. However, a possible explanation stems from young participants' near-ceiling accuracies, on average greater than 90%, during both conditions. Separately, the fact that older participants who made smaller localisation errors were also able to use the retro-cues better in order to improve could reveal a connection between selective WM retrieval and internal attention and its preservation with ageing.

This study's greatest dose of innovation stems from the findings pertaining to the effect of retro-cues in LTM. These suggest that retro-cues can significantly improve the quality of LTM memory retrieval, by reducing the number of guesses and improving localisation precision for both young and old adults. What is more, young individuals were able to benefit

more from the use of selective attention to improve their localisation errors, while still performing better overall compared to elderly individuals. This is the first study to show that retro-cues are also effective in LTM not only for young, but also for elderly adults. Building on previous work in the research group (Roüast, 2021), this is, to my knowledge, also the first study to develop a means of measuring the effect of orienting attention internally in both WM and LTM using equivalent materials and equitable tasks that allow for comparisons and investigations of different patterns of use not only across the two memory systems, but also across ageing. This was achieved by adapting the successful retro-cueing approach to measure LTM performance, to look at spatial-contextual associations that are also relevant and sensitive to ageing deficits. What is more, the tasks were designed to benefit from precision-based responses, allowing some modelling and greater control over sources of errors.

Comparing the way the two memory systems benefitted from retro-cueing, we observed different patterns. While in WM access to memories improves, as evidenced by higher accuracies in identifying the target objects and slower identification response times, the resolution of memory retrieval was enhanced in LTM, represented by lower localisation errors stemming from fewer guesses and increased precision. The differences in the way retro-cues benefitted WM and LTM could stem from the differences between the two memory systems. On one hand, localisation error may simply be a more sensitive measure of LTM retrieval. This could especially be the case for elderly adults, as their medial temporal lobe-based binding abilities decline. What is more, a fundamental difference exists between the two systems: whereas WM maintains a limited amount of information that retro-cues aim to filter based on task relevance, LTM, like perception of the external world, provides a much wider pool of information and stimuli to select from. Lastly, the two memory systems are mediated by retro-cues in different brain states: while the cues are provided during active simultaneous WM maintenance of information, retro-cued information from LTM is outside of the scope of attention and maintenance and solely mediates retrieval processes. These could be some of the underlying causes of the different patterns of retro-cueing mediation of retrieval between the two memory systems identified in this study.

Another result indicating differences between the use of retro-cues by the two memory systems is the lack of correlations between the retro-cueing benefits between WM and LTM, particularly in elderly adults, as well as the age-related differences in the patterns of retro-cues benefits. The relationship between retro-cueing benefits in WM and benefits in LTM was significantly different between the two age groups, younger adults showing a strong positive correlation which drastically weakened in ageing. The reason for these differences may reflect involvement of brain networks that are differentially susceptible to ageing decline. WM is known to rely, not only on the medial temporal lobe, but also on the prefrontal cortex for encoding, maintenance and manipulation of the information (D'Esposito, Postle, & Rypma, 2000). This could be a possible explanation, assuming the different rates of impairment of the two structures could lead to an erosion in the strength of correlations in old age. Additionally, LTM retrieval relied on a separate encoding task. The strength of encoding likely differed between the two age groups, as indicated by the learning results.

The principal goal of the current study was to investigate whether younger and older adults could use retro-cues to improve their LTM retrieval performance. Indeed, we found that young adults can use internal selective attention towards improved LTM performance and that these benefits are preserved in ageing, despite a change in the patterns of use. This finding represents a gateway to numerous research questions. First, future studies should investigate the underlying mechanism of retro-cueing in LTM. Is it relying on the same structures as in WM, or are they different? EEG, eye tracking and fMRI represent useful tools for this investigation. Using neural measures could help identify any anticipatory biases towards the retro-cued target prior to the presentation of the probe array in LTM. Functional neuroimaging techniques with greater spatial resolution could also be useful in measuring the extent of overlap between external attention and selective internal attention within LTM. Retro-cueing WM studies have previously observed additional activation of prefrontal regions (Nee & Jonides, 2009; Nobre et al., 2004) which leads to wondering how much the network in control of external goal-based spatial attention (Kastner & Ungerleider, 2000) also contributes to orienting attention for improved LTM retrieval and whether there are other

areas, beyond those identified in WM studies, involved in selective LTM retrieval. In this case, a structure of interest is represented by the hippocampus with bidirectional connections to the parietal cortex (Cabeza et al., 2008). In this case, mechanisms of selective attention driven by the parietal cortex could modulate hippocampal LTM retrieval. In turn, this could initiate memory reactivation in parietal areas (Tarder-Stoll, Jayakumar, Dimsdale-Zucker, Günseli, & Aly, 2020). The current task also provides a solid basis for these experiments, as it allows a direct comparison of WM and LTM using identical, continuous measures of retrieval precision and quality.

Next, variations of this proposed task could also help reveal further underlying mechanisms of retro-cueing in LTM. For example, future studies could investigate the effect of different delays between the presentation of the memory array in the LTM task and the appearance of the cue. In particular, future research could explore whether the cues are acting on LTM retrieval, or whether the retrieval of that specific episode was achieved by presenting the memory array, in which case the cue would be acting on material retrieved in WM, Previous studies have reported that recognition of encoded items correlates with a positive ERP wave observed between 500-800ms after item presentation called the "late positive component" (Düzel et al., 1999; Mecklinger, 2010). In this case, considering that the delay between the array presentation and the cue was 250ms, the retro-cueing effect should, in theory, act on the retrieval of items in LTM. However, further ERP studies could investigate how this effect would change if the delay was prolonged.

What is more, certain theories aiming to explain the mechanism of WM retro-cueing suggested an impairment in the memory for non-cued items and memory costs for invalid-cued items (Souza & Oberauer, 2016). Would this also be the case in LTM? The current task could also provide a basis for future experiments, that could also include invalid cues to determine their effect and tease apart different mechanisms of use. An additional free recall task could also be used to assess and compare participants' memory for differently cued items (Korkki et al., 2020).

Among the drawbacks of the current study is the relatively low trial number for each condition. In particular, these small number of trials were a limiting factor for the three-parameter two-dimensional mixture model fitted to the localisation error data to tease out the sources of participants' errors. Previous studies have showed that the higher number of trials the better the accuracy of the model (e.g., (Grogan et al., 2020)). For this reason, a subsequent follow-up study would benefit from increased trial numbers.

Additionally, a future adjustment to this paradigm design should include recall for the object-location associations encoded during the learning part of the LTM task. The measures used to quantify and confirm that learning was achieved are not fully reliable, as they could be modulated by participants' dexterity using a computer or their interest and motivation in taking part in the experiment. This additional measure could provide an indication on the quality of their encoding and confirm that significant learning was accomplished. What is more, this could also provide information about any effects related to prior probing and cue condition, revealing whether retro-cues strengthen the memory for target items and erode the quality of non-target retrieval.

This is the first human study to investigate and compare the effect of retro-cueing on memories of different timescales in two age groups using equivalent sensitive continuous report measures. The findings suggest that, despite the impairing effect of age on both working and long-term memory, both groups maintain the ability to use internal selective attention to benefit different aspects of their retrieval in WM and LTM. Additionally, the patterns of use of this orienting mechanism seems to differ between the two memory systems, and their relationship is altered by the passing of time. This study opens a line of research on the possible differences and similarities of the two processes as well as their underlying mechanisms and development across ageing.

3. Spatial memory and navigation in healthy ageing

Abstract

The ability to form spatial associations is a common feature of WM and LTM and a fundamental tool in our daily lives, and it is well established by now that performance of spatial memory and navigation typically decreases in ageing. However, the modulating effect of memory timespan and the interaction and interplay of WM and LTM have not received much attention so far. The first study presented acknowledged the importance of using optimal means to measure spatial memory and navigational abilities when testing special populations. It compared the performance of young and old adults in a spatial memory task on two devices – a personal computer (PC) and an immersive VR device – and measured whether the increased level of immersion benefitted older adults. Although the results were not generalisable due to several limitations in the testing procedures, they suggested that PC tasks were sufficiently appropriate to measure spatial memory in older populations and offered important lessons for designing the tasks in the second study of this Chapter. In the second study, a new PC-based navigational task was developed and used to measure and compare young and old individuals' associative abilities in WM and LTM at different delays. They were asked to learn and retrieve locations of distinct objects within different 3D environments. The results propose that, besides the damaging ageing effect on both memory systems, old individuals show significantly more forgetting that is likely unrelated to an increase in mis-binding errors. Future research should further explore these different patterns, as they have the potential of becoming markers of unhealthy ageing.

3.1 Introduction

Space represents a fundamental dimension along which we organise our perception of the world and, subsequently, our memory for locations and contexts associated with specific

experiences. Spatial memory for object locations and places, and navigation, our ability to find our way to them, are essential for effective everyday functioning, ensuring our mobility and independence. For example, a common everyday task is searching for our keys before driving towards a set destination. This relies on different skills and memory systems, which we employ at different stages of the task. The cognitive functions recruited for the successful retrieval of the keys' location represent the focus of Chapter 2. Once we have found the keys, we need to recall where we parked the car and navigate to the remembered location. As such, our navigational abilities and spatial memory represent a critical behavioural task and will be the focus of the current Chapter.

The increasing interest in spatial memory and navigation started in the post-HM era when the medial temporal lobe (MTL) and the hippocampus were placed under the spotlight by an extensive body of research investigating their role in declarative memory. Among the discoveries, the hippocampus was shown to be critical for a normal perception of space. It all began with the discovery of "place cells," hippocampal neurons that fire when a rat is in a particular location in the environment, and with findings suggesting that hippocampal damage causes deficits in some aspects of spatial memory in rodents (J. O'Keefe & Dostrovsky, 1971; John O'Keefe & Nadel, 1978). Since then, several other spatially modulated cell types have been identified, including grid cells, head direction cells, border cells, and speed cells (Kropff et al., 2015; Shine et al., 2016; Solstad et al., 2008; Taube, 2007). These cells have been identified in several mammalian species from humans and non-human primates to mice and bats (Ekstrom et al., 2003; Feigenbaum & Rolls, 1991; McHugh et al., 1996; Ulanovsky & Moss, 2007). Successful navigation is thought to be the result of the combined computations of these cells that generate a cognitive map (Tolman, 1948).

Within the field of spatial navigation, two distinct types of frames used to represent information about the environment have proven important: the egocentric frame, which refers to the placement of stimuli within the environment in relation to the self, and the allocentric frame, which refers to the location of the stimuli relative to each other, independent of self

within the external environment (Burgess et al., 2004; Colombo et al., 2017; Howard & Templeton, 1966; A. D. Milner & Goodale, 1992). A vast number of studies investigating the neurobiological correlates of the two navigational frames agree on the findings that the allocentric frame is mainly supported by the hippocampus and parahippocampal cortex, whereas the egocentric frame relies mainly on the striatal system (Aguirre et al., 1996; Cook & Kesner, 1988; Iaria et al., 2003; J. O'Keefe & Dostrovsky, 1971). Moreover, there is consensus among most authors that the successful formation of spatial representation needed for navigation in real life is not based on the use of one type of frame (Burgess, 2006). Instead, it relies on the ability to switch and combine different strategies flexibly, according to environmental requirements.

In returning to our earlier example, it becomes obvious that the features mentioned so far are some of the tools that combine to ensure our ability to navigate to the remembered location of our car. However, this process could be compromised in healthy ageing, reducing one's autonomy and quality of life. In fact, the structures that support spatial memory and navigation are among the first to undergo age-related neurodegenerative changes, which can act as indicators of a progression towards Alzheimer's Disease (Bates & Wolbers, 2014; Braak & Del Tredici, 2015). For this reason, an extensive body of literature is dedicated to understanding these changes and the way they affect spatial abilities, as they could become valuable tools for disease detection and interventions (Iaria, Palermo, Committeri, & Barton, 2009; Moffat, 2009). Many studies have shown altered computations in relevant neural networks that change the way older individuals process sensory information, form spatial representations, and plan and control their behaviour for navigation.

For example, older individuals have shown difficulties in allocentric compared to egocentric navigation tasks, as well as preferences for egocentric strategies (Head & Isom, 2010; Rodgers, Sindone, & Moffat, 2012). Such shifts in navigation strategy selection and preferences, also correlate with a shift in the use of environmental cues, with older adults relying more on proximal rather than distal cues (Schuck et al., 2013).

Body-based inputs such as vestibular and proprioceptive cues, motor efference copies, optic flow, and characteristics of the environment layout such as boundaries and landmarks serve as additional important guidance features during active navigation (Nardini, Jones, Bedford, & Braddick, 2008; Yoder & Taube, 2014). These enable the tracking of one's own location and orientation relative to the environment. Older adults, however, can struggle with adjusting the sensory weights of different bodily signals and show increased multisensory integration (Kuehn et al., 2018). In line with these findings, using a real-life navigation task while controlling for different sensory navigational cues, Bates and Wolbers (2014) showed that older adults had higher response variance and performed less accurately across conditions, placing less weight on the influence of landmark cues than would have been optimal to perform the task efficiently (Bates & Wolbers, 2014).

To retrieve and return to a previously visited location successfully requires recognition of landmarks encoded during learning, the sequence in which they occurred, as well as the associated directional information. Using an adapted version of the water maze to test older adults' memory of the landmarks in a virtual environment, Head and Isom revealed an association between ageing an inaccurate binding of directional knowledge to landmarks. In this experiment, they also showed ageing adults' impaired memory of the sequence in which landmarks were encountered (Head & Isom, 2010).

Given the challenges imposed by healthy ageing discussed thus far, the methods chosen to measure spatial memory and navigation become essential for collecting reliable data, with enough ecological validity to be representative for real life. Research on spatial cognition took an important step forward when virtual reality (VR) technology was introduced to the field. Here, VR refers to computer-generated 3D environments where participants can navigate, regardless of the viewing condition – that is, on a 2D computer screen or in an immersive fashion using a head-mounted display. On one hand, immersive VR enables the coupling of sensory and movement information to be recorded in ecologically valid, complex environments that mimic real life. On the other hand, computer-based VR can be paired safely

with human brain-imaging techniques (Diersch & Wolbers, 2019). Furthermore, VR studies not only provide access to realistic testing environments, but also offer the possibility of going beyond reality by manipulating experimental conditions and participants' locations within an environment without the need of physical relocation.

When drawing conclusions from VR studies, however, it is important to be aware that navigation in VR is not equivalent to real-world navigation (Taube, Valerio, & Yoder, 2013). Unlike in real life, the main sensory input in most VR tasks comes from the visual system, and movement is simulated by changes in optic flow while the navigator's body is static. For example, Ruddle and colleagues showed that participants' ability to recall locations in the environment is better for those who physically walk in VR than for participants who only use a joystick to navigate (Ruddle, Volkova, & BüLthoff, 2011). However, more recently, Coutrot and colleagues found that navigation within a virtual environment tested using a mobile app is predictive of real-world wayfinding navigation performance, taking another step towards more sensitive, safe, low-cost, and accessible assessments of navigation ability (Coutrot et al., 2019).

The use of VR for testing older adults is still in its infancy. So far, research suggests that the effects of age on spatial abilities are comparable between VR and real-world tasks, although performance in VR is often generally decreased (Diersch & Wolbers, 2019; Taillade et al., 2016). Testing an ageing population in VR comes with additional concerns. First, older adults are typically less experienced with using new technologies compared to younger adults. Consequently, they might experience elevated levels of stress and anxiety during testing, exacerbated by their desire to perform well and make a good impression when watched by the researcher (Barnard, Bradley, Hodgson, & Lloyd, 2013). Second, older adults have also been shown to be more susceptible to cybersickness, a side-effect similar to motion sickness, consisting of headache, nausea, and eye strain (Arns & Cerney, 2005).

The aim of the first study presented in this chapter was to compare the performance of two groups of young and older healthy adults in a spatial memory task on two devices – a

personal computer (PC) and an immersive VR device – and to measure whether elderly individuals benefit from an increased level of immersion. As discussed, impaired spatial memory is one of the first symptoms of hippocampal damage and therefore, when tested using optimal methods, could become a useful marker. The experimental approach builds on the findings reviewed above and relies on an allocentric spatial memory task analogous to a virtual water maze. In addition, it introduces the innovation of using tasks with identical environments, stimuli, and response requirement to compare performance between the two devices.

Considering the network changes and corresponding behavioural decrease in performance in previous studies, I expected to find an overall better navigation performance of young compared to elderly adults on both devices. Based on previous literature showing that older adults tend to rely more on body-based and sensory inputs for navigation, I also expected them to perform better in the immersive version of the task compared to the 2D PC version. Furthermore, the benefits might be smaller for young adults as their performance could be modulated by their experience with similar technology. Lastly, this study also aimed to inform subsequent investigation into different aspects of spatial memory in ageing discussed below.

Building on the dichotomy between WM and LTM proposed in Chapter 1, and elaborated in Chapter 2, the spatial aspect of these memory systems is of great interest. There is consensus regarding the overall decrease in performance of spatial memory and navigation in ageing (Korkki, Richter, Jeyarathnarajah, & Simons, 2018; Pertzov et al., 2015; Salvato et al., 2016). However, the modulating effect of the post-encoding delay and the interaction and interplay of the two memory systems have not received much attention so far.

Considering the role of space in remembering objects' locations, Pertzov and colleagues (2015) tested how object-location binding performance is influenced by aging in WM. They used an object-location task in which participants were presented with either 1 or 3 fractal objects for a period of 1 or 3 seconds and were instructed to remember both the

objects' identities and their locations. After a delay of either 1 or 4 seconds, they were asked to choose between two objects, one of which was presented previously and the other was a lure, and then drag it to its remembered location using their finger. Their findings indicate a decrease in localization performance for older adults, but no changes in object-location association retrieval with increasing age (Yoni Pertzov et al., 2015).

An object localisation precision deficit in ageing has also been established in LTM. Chalfonte and Johnson (1996) presented young and old participants with arrays of coloured objects and asked them to encode either the colour, location or identity of the objects. Next, individuals' recognition memory for the features they were instructed to study was tested. They found that older adults showed a significant deficit in recognition memory for location, but not for item or colour compared to younger adults (Chalfonte & Johnson, 1996).

More recently, Salvato et al. (2016) were also able to replicate the decrease in object localisation precision in ageing in LTM. During the learning phase of the task, participants were first presented with a target object and then they were asked to locate the object in a scene and memorise its location. After a 30-minute break, participants performed a memory-guided spatial orienting task, followed by an explicit recall of the objects' identities and locations within the scenes. This study similarly found significant deficits in the explicit retrieval of object locations (Salvato et al., 2016a).

Despite these deficits being established separately for the two memory systems, a spatial memory or navigational perspective has not yet been considered when investigating the interplay and dissociations of WM and LTM. What is more, using different tasks to quantify WM and LTM, despite using equivalent measures, could introduce difficulties in drawing comparisons, as each task might present different limitations. Considering the sensitivity of such memory measures for cognitive decline with ageing, comparing WM and LTM using the same task becomes particularly important, as it could reveal different memory patterns of the same content.

Therefore, building on knowledge acquired in the previous study and on previous research, for the second study in this chapter I used a spatial memory task within a navigational setting that incorporated measures of both WM and LTM, as well as the patterns of dissociation and interplay that might change with ageing. Moreover, LTM was measured at two timepoints, both 20 minutes after encoding and the next consecutive day. I expected to find a decrease in spatial abilities for both WM and LTM in older adults. Additionally, I anticipated that I would find a correlation between WM and LTM in young adults, but not in older adults. Lastly, I predicted a decrease in memory quality with time for both age groups.

3.2 Optimal methods of probing spatial memory in ageing

3.2.1 Methods

3.2.1.1 Participants

This study was approved by the Central University Research Ethics Committee (CUREC) (research ethics project number: 08/H0606/133). All participants provided their informed consent prior to taking part in the study and were reimbursed for their time at a rate of £10/hour, as well as for their travel to the testing venue.

Healthy young participants were University students recruited to take part in this study via advertisements on social media platforms and college newsletters. Elderly participants were volunteers from the general population in the Oxfordshire area, recruited from the participant database of the Memory Research Group and by distributing flyers around Oxford. Overall, 21 healthy young and 18 elderly adults volunteered to part in this study. However, seven elderly participants experienced nausea and disorientation while performing the task in the immersive environment. They withdrew from the experiment and their incomplete datasets were excluded from the data analysis (see section 3.2.2 in the Results). Complete datasets were collected from 21 healthy young adults (9 females, 12 males, age range 21-31, M = 26.3, SD = 3.3) and 11 healthy elderly adults (5 females, 6 males, age range 60-79, M = 65.4, SD = 6.7).

The Addenbrookes Cognitive Assessment III (ACE) (Hsieh et al., 2013) was administered to all participants. This is a neuropsychological test used to identify and measure cognitive impairment. A total score above 88 typically translates to an absence of clinical cognitive impairment. Participants' results and a comparison between the two age groups on their ACE III scores can be found in Table 3.1 in the Results section.

3.2.1.2 Experimental setup

Testing took place in a large, quiet open hall, without natural light. Participants performed the same behavioural task on two different devices. One of the devices was a Dell Latitude E7450 laptop (PC) with a 13" display, placed on a desk. While completing the PC version of the task, participants were seated at the desk, approximately 60 cm away from the screen, and navigated within the task environment using the WASD keys on the laptop keyboard and a Logitech Extreme 3d Pro joystick (Figure 3.1).

Participants also performed the task on a Google Project Tango virtual reality (VR) tablet that enabled an immersive experience. This device had a 180° fish-eye camera for feature recognition and an accelerometer, a gyroscope and magnetometer for motion tracking. It used an Android operating system, and a Nvidia Tegra K1 processor. It had a 7.02" 1920 x 1200 high-definition display used to project a virtual world to the participant. The tablet was mounted within a Durovis Dive headset, which was adjusted until the participant was comfortable and the device could accurately track the participant's movement (Figure 3.1). Mounting of the device left two gaps on either side of the headset, which could potentially disrupt the immersive experience, as they were avenues for additional light and confounding visual stimuli. For this reason, they were covered using opaque, grey duct tape which blocked the light. The tape was only stuck on the headset and did not contact participants' skin. A Durovis Dive plug-in programmed in the task allowed a naturalistic stereoscopic three-dimensional view.

The testing hall had sufficient real-world salient features to allow accurate motion tracking. Participants' virtual perspective changed as they were moving in the real world. While completing the task in VR, the researcher walked a few steps behind the participants, both to monitor their balance, and to provide verbal instructions from a constant distance, without the voice acting as an auditory cue for location. The hall's carpeted floor muffled footstep noise from acting as a confounding factor and there were no other sources of ambient noise. Participants verbally indicated when they reached the desired position (e.g., when they reached the target object location), and the researcher would record their response using a portable wireless controller for the device (Figure 3.1). The same procedure was used for both young and elderly participants.



Figure 3.1: Testing equipment for the two devices. (A) When performing the task on the PC, participants navigated on a Dell Latitude E7450 laptop, using a Logitech Extreme 3d Pro joystick and the WASD keys on the laptop's keyboard. (B) When performing the task on the VR device, participants were immersed in the environment using a Google Project Tango virtual reality tablet mounted on within a Durovis Dive headset; they navigated by walking in the real world and, to make responses in the task, they verbally indicated when they reached the desired position (e.g., when they reached the target object location), and the researcher would record their response using a portable wireless controller.

3.2.1.3 Protocol

The testing protocol consisted of the Addenbrookes Cognitive Assessment III (ACE-III) followed by the same spatial memory task performed consecutively, after a 5-minute break, on the PC and on the VR device. The order of the devices was counterbalanced across participants.

After completing the task on both devices, during the debriefing session, participants were asked about their device preference and the strategies they used when navigating to the remembered locations in the environment.

3.2.1.4 Behavioural Stimuli

During the task, participants searched for and remembered the location of three different objects, which varied between the two environments: a teddy bear, a fire extinguisher, and a crib on the PC; and a snowman, a present and a hydrant on the VR device (Figure 3.2). All objects are available on the Unity asset store and their dimensions were set to have an equal size of 0.5 virtual meters (vm). The objects always appeared at the ground level, with a z coordinate of 0. Different objects were used in the PC and VR to limit interference across tasks. The object-device pairings were consistent across participants. The location of each object remained consistent throughout the task and across participants, but they were different between the two testing modalities.

A)



B)



Figure 3.2: Individual object stimuli used for the spatial navigation task on each of the two testing modalities. (A) The three object stimuli participants encoded and retrieved in the task on the PC: a teddy bear, a fire extinguisher and a crib. (B) The three object stimuli participants encoded and retrieved in the task on the VR device: a snowman, a present and a hydrant.

The environment in which participants searched for these objects was identical on the two devices. Each object position was originally generated such that each object was in a different quadrant of the environment and remained the same throughout the experiment. These positions were identical for all participants.

The virtual environment was developed to provide a first-person perspective of an outdoor scene consisting of a circular arena with distal landmarks. The virtual world was designed using the Unity Games Engine v5.3.4f in C#. The circular arena had a radius of 6 virtual meters (vm), and a repetitive amorphous cobblestone floor lit in a way that it would not provide additional intra-arena cues. This was enclosed by a 0.3 vm high impenetrable boundary. Distant landmarks consisted of a tropical forested mountain, a volcanic peaked mountain, a snow-covered hill, and a city scape as well as a cloudy sky (Figure 3.3). Distal landmarks were rendered such that they appeared far in the distance and did not draw closer to the participants as they navigated. This ensured that distal landmarks only provided cues to direction and orientation, but not to location and distance.

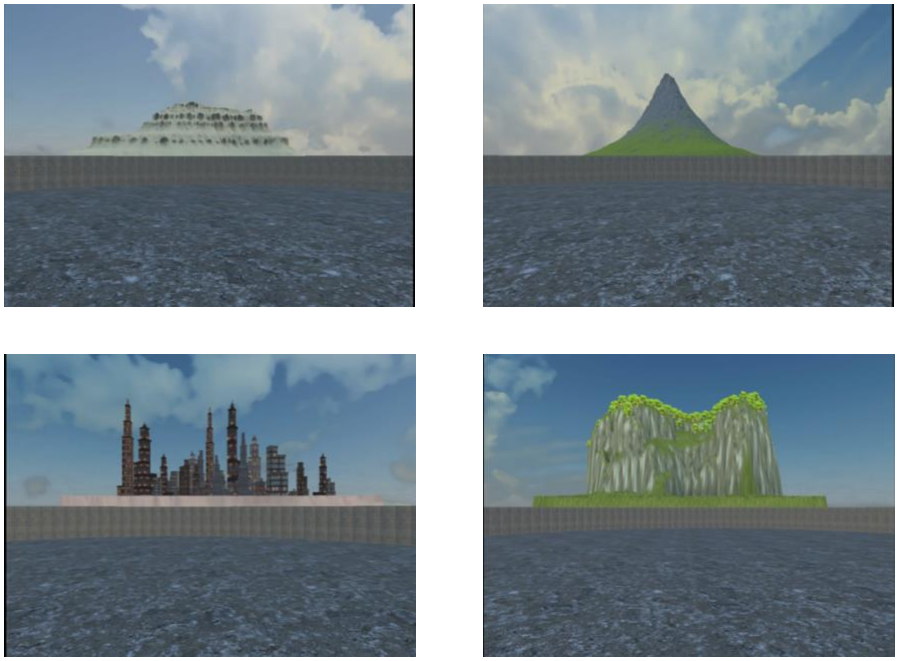

Figure 3.3: Screen captures of the task environment depicting the fours distal cues (a snow-covered hill, a volcanic peaked mountain, a city scape and a tropical forested mountain), as well as the repetitive amorphous cobblestone floor and the impenetrable boundary surrounding the arena.

3.2.1.5 Behavioural Task

Spatial memory was assessed using a task in which participants had to keep in mind the location of everyday objects within a bounded circular arena. Participants were informed that they would search through the same arena for three different everyday objects, with one object appearing per trial, and that their goal was to remember their locations. The object identities were not revealed before the start of the task, although they were conspicuous and readily recognised. To start, participants were given time to explore the environment without any objects until they felt comfortable using the technology. Subsequently, testing was arranged into three phases: encoding, practice and retrieval (Figure 3.4).

3.2.1.5.1 Behavioural Task on the PC

In the encoding phase, participants were instructed to navigate through the arena using the joystick and laptop keyboard until they identified the target object. They were then asked to indicate when they reached the object location by clicking on the trigger button of the

joystick. If they were within 1 vm from the object, the screen faded to black, and the next trial began. If they were further from the object, they had to navigate until they were below the 1 vm threshold and respond again (Figure 3.4). The encoding phase consisted of three blocks, within which the three objects were presented in random order across participants once.

During practice, once in the start location, participants were shown an image of an object from the encoding phase at the top right corner of the screen. They were instructed to navigate to the remembered location of the respective object using the keyboard and joystick. Once they indicated the position using the trigger button on the joystick, they received feedback on their accuracy. If the recalled position was within a 1 vm radius of the correct object position, the word "correct" appeared in blue, along with a green light effect. If the recalled position was outside of this threshold distance, an "error" message in red text was displayed. Additionally, the target object also appeared in its correct position, irrespective of the participants' accuracy and they had to navigate there and make a response, as they would in encoding trials. If they were already in the correct location, they were instructed to make a response to move on to the next trial (Figure 3.4). The practice phase consisted of four blocks, within which the three objects were presented in random order across participants once.

The last phase of the task involved retrieving the location of the objects in the arena in the absence of feedback. The stimuli and procedures were the same as for the practice phase except that the objects did not reappear within the arena after the participants responded. Participants were instructed to retrieve the location of the object cued in the top right corner of the screen and indicate using the joystick when they reached the correct location. Once they made a response, the next trial began (Figure 3.4). The retrieval phase consisted of four blocks, within which participants retrieved the three objects in random order once.

For the beginning of each trial during the three phases of the task, participants started in different, pseudo-randomised locations which presented different perspectives within the arena to ensure navigation relied on allocentric cues and memory.

3.2.1.5.2 Behavioural Task in VR

In the VR version of the same task, three different objects were used and presented in the same environment. To navigate, participants simply walked in the real world. The structure of the task was same as on the PC (Figure 3.4), but the way participants responded required several adaptations.

First, in the encoding phase, participants were asked to explore the arena by walking around, until they identified the target object. They verbally indicated when they reached the object location, and the researcher used a wireless controller to make a response. Next, during practice, participants were presented an image of an object from the encoding phase on the top right side of their field of view and they were asked to navigate to the remembered location of the object by walking. Similarly, once they verbally indicated they reached the location and the researcher made a response, they received feedback on their accuracy. If the recalled position was within a 1 vm radius of the correct object position, the word "correct" appeared in blue in front of them, along with a green light effect. If their response was outside of this threshold, an "error" message in red text appeared. Furthermore, compared to the PC, participants responded during retrieval by verbally indicated when they reached the remembered location.

The last adaptation for the VR device consisted of the different method of assigning the participants' start position. At the beginning of each trial, participants were placed in a different, pseudo-randomised location showing a different perspective of the environment. Since participants could not be artificially 'dropped' into an arbitrary location in the real world, as this would disrupt the relationship between the boundaries of the virtual world and the real world, their position in the virtual world could not be completely random. Therefore, the participants' start position was chosen as a random point on the circumference of a circle whose centre matched that of the virtual environment, and radius was equal to the distance between the centre and the participant's location. This way, the participant's viewpoint in the

environment was rotated such that their relationship with both the real and virtual boundaries was consistent.

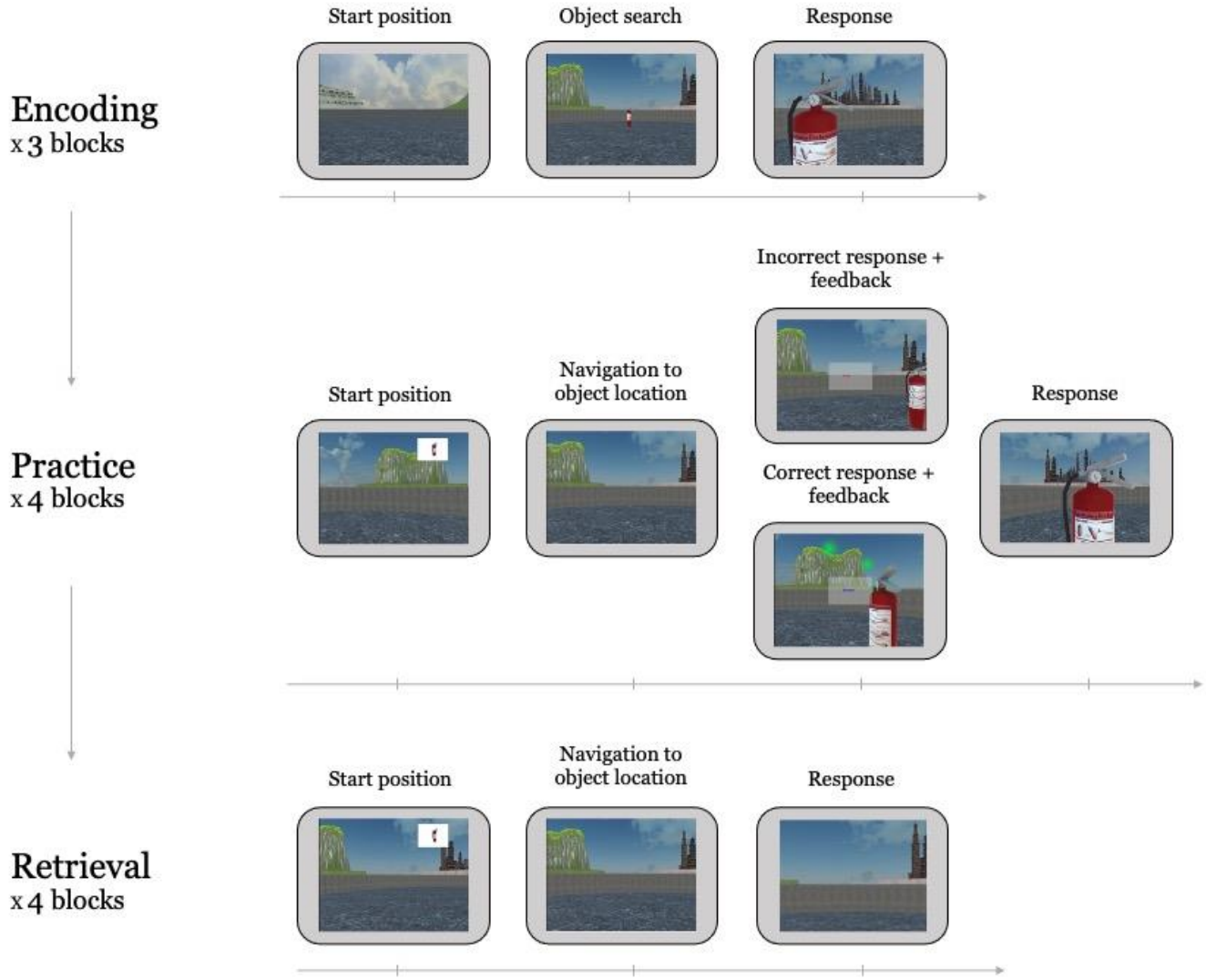

Figure 3.4: A schematic of the task design used on both testing modalities (PC and VR), consisting of encoding, practice and retrieval blocks. This schematic illustrates the task timeline for one of six everyday objects used overall for this experiment. During encoding trials, participants searched for the target object by navigating through the environment and they responded once they reached its location. After 3 blocks, the practice phase started where participants were asked to retrieve and navigate to the previously encoded object locations. Once they made a response, they received feedback on their performance and the objects appeared in the correct location. They were asked to make an additional response when they were in the indicated correct location. Lastly, the retrieval phase involved retrieving the location of the objects in the arena in the absence of feedback.

3.2.1.6 Behavioural Analysis

The same dependent measures were computed for both task modalities (PC and VR) and included accuracy, distance error and path efficiency. For comparison, the coordinates were mapped onto an equivalent metric aligned to virtual meters.

Accuracy was calculated for the retrieval phase as the % of trials in which participants responded correctly, meaning they were within 1 vm from the target location, out of the total number of trials they performed. The following formula was used:

Accuracy (%) = Number of correct trials x 100 / Total number of trials

Distance error was calculated as the Euclidian distance from the position indicated by the participant as their response and the correct position of the respective object in virtual meters. This measure was used to analyse participants' performance on practice and retrieval trials.

The last dependent variable was path efficiency, which was computed using the following formula:

Path Efficiency = (Path Length) / (Shortest Path)

Path length was measured as the total distance navigated by a participant within a specific trial. The shortest path was the Euclidian distance from the participant's start position and the correct location of the object, meaning the shortest straight line drawn between the two points. Path efficiency was computed only for retrieval trials.

Data were initially processed in Matlab ver. R2018b, where the coordinates for each trial were extracted from the recorded files. The 1.5 s of data between every two trials, consisting of the screen fading to black during the inter-trial interval, were removed. If any irregularities were noted (such as program errors, or accidental button presses from the participant) during the participants' performance, that trial was excluded from further analysis. The minimum number of trials per participant was 9 for the practice phase and 9 for the retrieval phase. If participants did not complete sufficient trials, they were excluded from

the analysis. A total of 3.4% retrieval trials were removed for elderly participants, and 0.8% of retrieval trials were removed for young controls.

Data were then analysed using the R software. Mixed-model ANOVAs with device and block as within-subject factors and age group as a between-subjects factor were used to analyse practice performance. Similarly, mixed-model ANOVAs with device as within-subject factor and age group as a between-subjects factor were used to analyse retrieval performance. Prior to conducting these statistical tests, the assumption of homogeneity of variance was tested using Levene's test, whereas the normality of the distribution of the values was visualised using histograms, the values of skewness and kurtosis, and tested using the Shapiro-Wilk test. All assumptions were met.

3.2.2 Results

In the interest of completeness, both descriptive and statistical results are presented below. The current study was based on a small sample size and was therefore statistically underpowered. As described in the Discussion, during study implementation, several experimental limitations were noted, leading to early termination of the study. Accordingly, any statistical outcomes should only be interpreted in relation to this particular cohort and should not be the basis for any further generalisation.

3.2.2.1 Cohort Profiles

Complete datasets were collected from 21 healthy young adults (9 females, 12 males, age range 21-31, M = 26.3, SD = 3.3) and 11 healthy elderly adults (5 females, 6 males, age range 60-79, M = 65.4, SD = 6.7).

The Addenbrookes Cognitive Assessment III (ACE) (Hsieh et al., 2013) was administered to all young and elderly participants. Both groups scored within the expected range for healthy individuals (Yamada et al., 2019). The groups did not differ significantly in

their mean scores in any of the five cognitive domains (attention, memory, fluency, language and visuospatial abilities) (Table 3.1).

Table 3.1

Means and standard deviations of the Addenbrookes Cognitive Assessment III (ACE) scores of young and elderly participants. The two groups did not differ significantly in their mean scores in any of the five cognitive domains (attention, memory, fluency, language and visuospatial abilities).

	Young	Elderly	Significance (p)
ACE – Total, mean (SD)	96.7 (2.8)	96.1 (2.5)	0.5
ACE – Attention, mean (SD)	17.2 (1.5)	16.9 (1.9)	0.6
ACE – Memory, mean (SD)	25.1 (0.9)	25 (1.3)	0.9
ACE – Fluency, mean (SD)	12.7 (1.5)	13 (1)	0.5
ACE – Language, mean (SD)	25.9 (0.3)	25.9 (0.4)	0.9
ACE – Visuospatial abilities	15.9 (0.3)	15.4 (0.8)	0.1

Additionally, to estimate participants' familiarity with computers, PC usage data were collected during debriefing, once the task was completed on both devices. Participants were verbally asked how many hours a week they spent playing computer games. Young participants' response was three times higher than those of elderly participants. They also reported spending more time on their computers daily compared to elderly participants (Table 3.2).

Table 3.2

Means and standard deviations of the number hours young and elderly participants spend daily on the PC and the number of hours they spend gaming per week, indicating that young participants spend significantly more time in front of the computer compared to the elderly group.

	Young	Elderly	Significance (p)
h/day on the PC	8.1 (1.7)	3.6 (3)	0.001
h/week gaming	1.8 (2.4)	0.5 (0.9)	0.04

Participants were also asked about their device preference. A chi-square test of independence was performed to examine the interaction between age group and device preference. This test compares the frequencies with which the two groups preferred each of the two devices to the frequencies expected to be observed by chance for each age group. The results reflected a significant relationship between the two variables, indicating that young participants had a stronger preference for the VR device, unlike elderly participants (χ^2 (1, N = 33) = 13.4, $p < .001$) (Table 3.3).

Table 3.3

Participants' preference for performing the task on one device over the other.

Device preference	Young Participants	Elderly participants
PC	2	8
VR	19	3

Lastly, in the verbal debriefing session, when asked about the strategies they used to memorise and retrieve the target objects' locations, all elderly participants reported that they used the distal cues surrounding the virtual arena to guide them in the environment for both the PC and the VR task. Likewise, 18 of the 21 young participants reported the same navigation strategy. Of these 18, 7 also reported to have taken into account proximity to the fence enclosing the arena when making responses. In addition, two of the young participants stated that they counted the steps between a chosen landmark and the target objects when learning the objects' locations in the VR task, and one other participant reported forming mnemonic associations between the objects and the respective distal cues in their background.

3.2.2.2 Adverse Effects and Exclusion of Participants

Data collection was more problematic than anticipated due to technical limitations, and the usable dataset of elderly participants was small.

Overall, 18 elderly participants took part in this study. However, approximately 40% (seven) experienced nausea, headaches and disorientation while performing the task in the immersive environment and withdrew from the experiment. Their incomplete datasets were excluded from the data analysis, as the minimum number of trials per participant was 9 for the practice phase and 9 for the retrieval phase. Therefore, data from only 11 elderly participants were included in the final analysis presented below. None of the young participants complained of similar adverse effects in either of the testing modalities.

In addition to the adverse effects, elderly participants were less active in the immersive environment, only reaching the target in approximately 25% of the retrieval trials (Figure 3.6). Their lack of engagement with the VR environment is also evidenced by their low path efficiencies (Figure 3.8). These factors, along with additional technical and practical limitations involving the testing venue, led to the early termination of this study.

3.2.2.3 Practice Results

First, participants' performance was examined over the four practice blocks in which they received feedback after making a response. The mean distance error between participants' response and the target location was calculated and averaged across all objects and participants. On average participants' performance did not improve below the cut-off for accurate performance (1 vm) in neither of the two groups. A mixed-model ANOVA with age group as the between-subjects factor and block number and device as the within-subject factors showed a main effect of age group ($F(1,30) = 17.01$, $p < .001$, $\eta^2 = 0.09$), showing that young participants made smaller errors compared to the elderly group. Furthermore, age group and device interacted significantly ($F(1,30) = 4.89$, $p = 0.038$, $\eta^2 = 0.04$), reflecting the different modulating effect of the device on the two age groups' performance. Older people who completed the procedures performed better on the VR device, whereas young participants were better on the PC. However, there were no main effects of block number ($F(3,62) = 2.44$, $p = 0.073$, $\eta^2 = 0.01$) or device ($F(1,30) = 1.7$, $p = 0.205$, $\eta^2 = 0.008$), and no significant block

x group ($F(2,62) = 0.7$, $p = 0.555$, $\eta^2 = 0.01$), block x device ($F(2,62) = 0.72$, $p = 0.544$, $\eta^2 = 0.009$) or block x device x group ($F(2,62) = 1.01$, $p = 0.398$, $\eta^2 = 0.003$) interactions (Figure 3.5).

To investigate the significant device x group interaction further, paired-sample t-tests were performed for each age group, comparing their learning on the two devices separately. The tests indicated that learning between the two devices did not differ significantly for young participants ($t(20) = -1.34$, $p = 0.183$, $d = .2$). On the other hand, elderly participants made smaller errors in the VR environment compared to the PC ($t(10) = 3.9$, $p < .001$, $d = .3$) (Figure 3.5).

Additionally, an ANCOVA was separately conducted to control for the number of hours participants spend gaming per week. The results of the ANCOVA also showed a main effect of age group ($F(1,30) = 12.01$, $p = 0.02$, $\eta^2 = 0.07$), suggesting that young participants made smaller errors compared to the elderly group, even when considering their increased gaming experience. Furthermore, age group and device interacted significantly ($F(1,30) = 6.89$, $p = 0.01$, $\eta^2 = 0.09$), reinforcing the different modulating effect of the device on the two age groups' performance after controlling for the level of expertise in gaming. Older people' performance was better on the VR device, the more intuitive option, whereas young participants were better on the PC, likely aided by their computer gaming expertise. Lastly, there were no main effects of block number ($F(3,62) = 2.76$, $p = 0.08$, $\eta^2 = 0.02$) or device ($F(1,30) = 2.6$, $p = 0.09$, $\eta^2 = 0.01$), and no significant block x group ($F(2,62) = 1.3$, $p = 0.5$, $\eta^2 = 0.02$), block x device ($F(2,62) = 0.89$, $p = 0.44$, $\eta^2 = 0.01$) or block x device x group ($F(2,62) = 2.01$, $p = 0.1$, $\eta^2 = 0.01$) interactions.

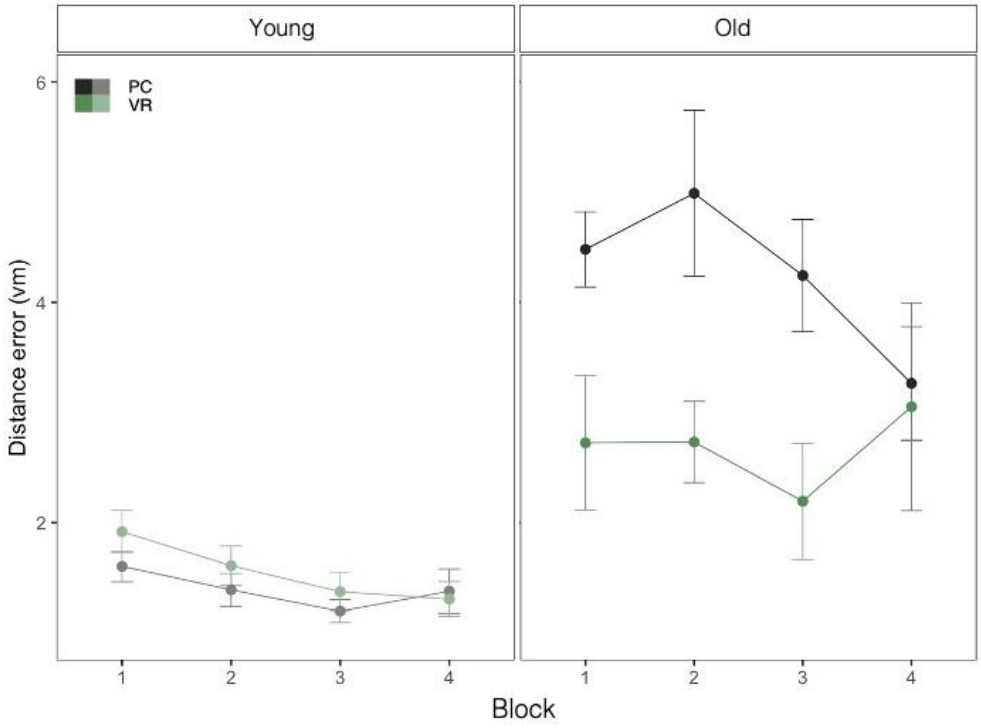

Figure 3.5. The two graphs show the average distance errors for each of the four learning blocks and both experimental devices. The error bars represent the standard error of the mean. This reflects the fact that elderly participants performed worse overall, but they benefitted more from the level of immersion in the VR, compared to younger individuals.

3.2.2.4 Retrieval Results

Next, participants' accuracies were computed as the percentage of trials in which they made a correct response and compared between groups and testing modalities. Accuracy means were collapsed over the multiple retrieval trials and objects. Overall, participants' accuracy was very low. On average young participants responded correctly on approximately 50% of the trials, whereas older participants retrieved the correct location for 20% of the trials. A mixed-model ANOVA with age group as the between-subjects factor and device as the within-subject factor revealed a main effect of age group ($F(1, 30) = 27.37$, $p < .001$, $\eta^2 = 0.45$), with younger participants responding correctly on significantly more trials compared to elderly participants. However, the main effect of device ($F(1,30) = 0.44$, $p = 0.511$, $\eta^2 = 0.01$) and the group x device interaction ($F(1,30) = 2.49$, $p = 0.123$, $\eta^2 = 0.07$) were not significant (Figure 3.6). Similar results were observed when controlling for gaming experience, The ANCOVA with number of hours spent gaming per week as a covariate, revealed a main effect

of age group ($F(1, 30) = 13.14.37$, $p = .01$, $\eta^2 = 0.42$), but no significant effect of device ($F(1,30) = 0.34$, $p = 0.7$, $\eta^2 = 0.03$), or group x device interaction ($F(1,30) = 5.23$, $p = 0.08$, $\eta^2 = 0.09$).

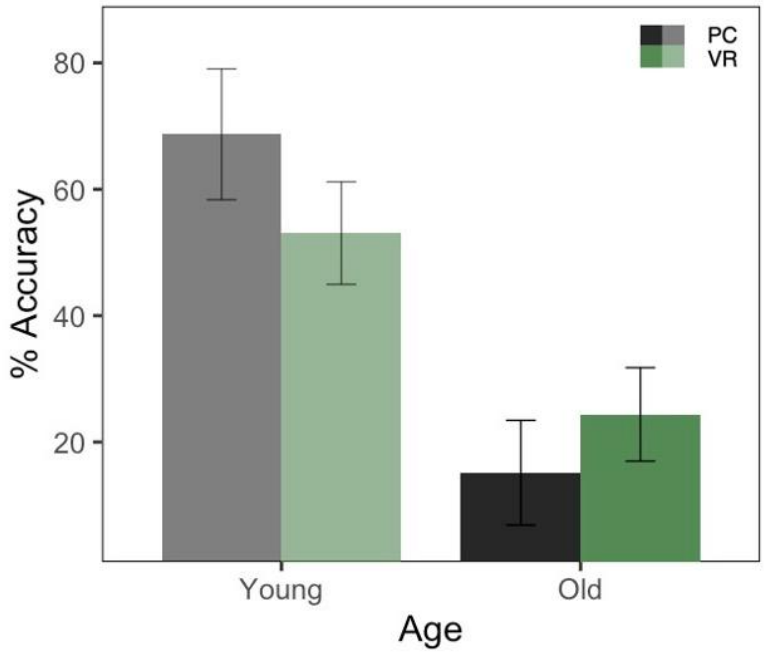

Figure 3.6. Average accuracies during retrieval for young participants on the left and elderly participants on the right, for both experimental devices. The error bars represent the standard error of the mean. The figure reflects that young participants responded correctly on significantly more trials compared to elderly participants.

Furthermore, the effect of the level of immersion on participants' distance errors during retrieval for the two groups and devices was investigated. Distance error means were collapsed over the multiple retrieval trials and objects. A mixed-model ANOVA with age group as the between-subjects factor and device as the within-subject factor revealed a main effect of age group ($F(1, 30) = 109.78$, $p < .001$, $\eta^2 = 0.18$), with younger participants performing better than the elderly. Moreover, a significant group x device interaction ($F(1,30) = 37.56$, $p < .001$, $\eta^2 = 0.07$) indicated that the two age groups performed differently on the two devices. The main effect of device was not significant ($F(1,30) = 0.28$, $p = 0.597$, $\eta^2 = 0.01$). Follow-up paired-sample t-tests showed that young controls made significantly smaller errors on the PC compared to the VR ($t(20) = -3.28$, $p = 0.004$, $d = .6$), whereas older participants did not differ significantly between the two devices (Figure 3.7). The two groups' distance errors were

compared between the two devices controlling for gaming experience, using the number of hours participants spent gaming per week as a covariate. The ANCOVA revealed similar results with a main effect of age group ($F(1, 30) = 88.62$, $p = .009$, $\eta^2 = 0.13$), with younger participants performing better than the elderly, as well as a significant group x device interaction ($F(1,30) = 17.16$, $p = 0.03$, $\eta^2 = 0.04$) suggesting that the two age groups performed differently on the two devices. The main effect of device was not significant ($F(1,30) = 0.68$, $p = 0.61$, $\eta^2 = 0.01$). Follow-up paired-sample t-tests showed that young controls made significantly smaller errors on the PC compared to the VR ($t(20) = -3.88$, $p = 0.008$, $d = .6$), whereas older participants did not differ significantly between the two devices.

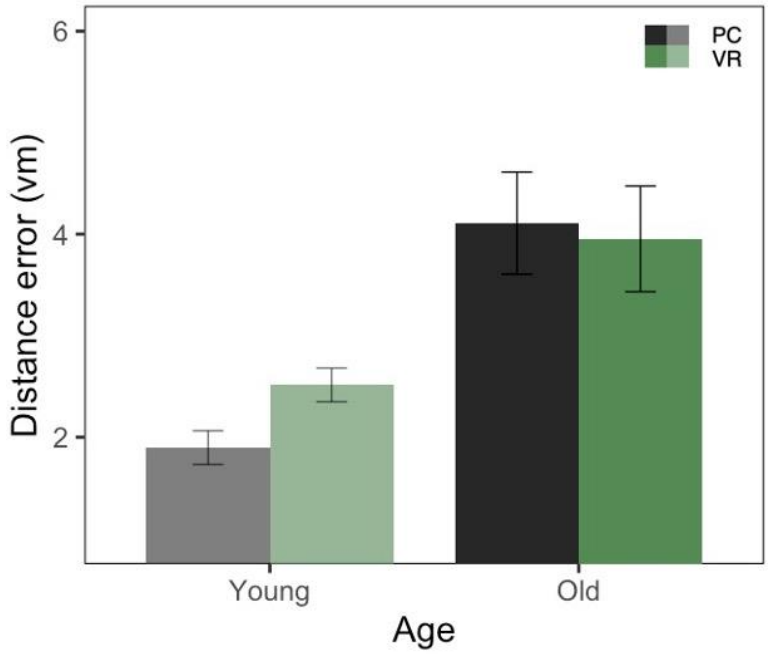

Figure 3.7. Average distance errors during retrieval for young participants on the left and elderly participants on the right, for both experimental devices. The error bars represent the standard error of the mean. The figure reflects that young participant made smaller errors, compared to elderly participants. Additionally, they also made smaller errors on the PC compared to the VR device.

To quantify the impact of the interference caused by the fact that the virtual environments were identical between the two devices on the groups' performance, the proportion of swaps between devices was calculated for each age group. This measure represents the proportion of retrieval trials where participants marked the location of the cued

object within 1vm of the correct position of one of the objects from the device they were not performing on at the time. The proportions of swaps were compared between the two age groups using an independent-sample t-test. This revealed that old participants swapped the locations of objects between the two devices significantly more than young participants ($t(20) = 2.35$, $p = 0.03$, $d = .5$) (Figure 3.8).

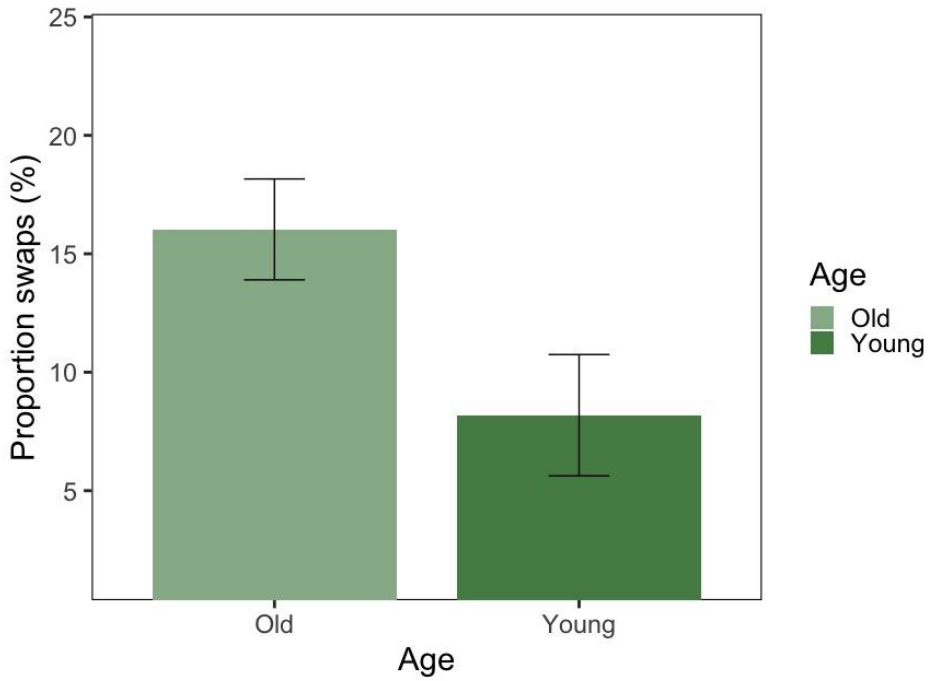

Figure 3.8. Average proportion of swaps of object locations between the two devices during retrieval for young participants and elderly participants. The error bars represent the standard error of the mean. The figure reflects that young participant made fewer swaps, compared to old participants.

Finally, path efficiency was computed as an indicative proxy of participants' engagement with the task environment, showcasing how much they explored the arena during retrieval, and compared between groups and devices. The values were collapsed across blocks and objects. In theory, a path efficiency of 1 indicates that participants' walked the same distance as necessary to reach the target location. If path efficiency is below 1, it means that participants walked a shorter distance than that necessary to reach the target and were not very engaged with the task. A value greater than 1 means that they walked a longer route, and their engagement with the environment tended to be higher.

The trials in which participants did not make a correct response, meaning they were outside of the 1vm threshold from the target location, were excluded from the analysis. Only trials in which participants reached the correct location are analysed below and included in Figure 3.9A. Considering the 1vm threshold within which responses are considered correct, some path efficiencies below 1 are included in the figure and in the analysis, because walking 1vm less than the perfect distance required to reach the target would yield a value below 1, despite being considered a correct response. Figure 3.9B shows example trajectories of both young and old participants on both devices, emphasising the lack of engagement with the task, particularly evident in old individuals.

A mixed-model ANOVA was performed with path efficiency as the dependent variable, device as the within-subjects factor and group as the between-subjects factor. The results revealed that neither the main effect of age group ($F(1,30) = 0.15$, $p = 0.699$, $\eta^2 = 0.001$) nor the main effect of device ($F(1,30) = 0.55$, $p = 0.459$, $\eta^2=0.001$) were significant. The device x group interaction showed a non-significant trend ($F(1,30) = 3.46$, $p = 0.065$, $\eta^2 = 0.03$) (Figure 3.9 A). This suggests that, when responding correctly, young and elderly participants reached the target location with similar efficiency in both testing modalities. These results are also illustrated in the example retrieval trajectories below (Figure 3.9 B).

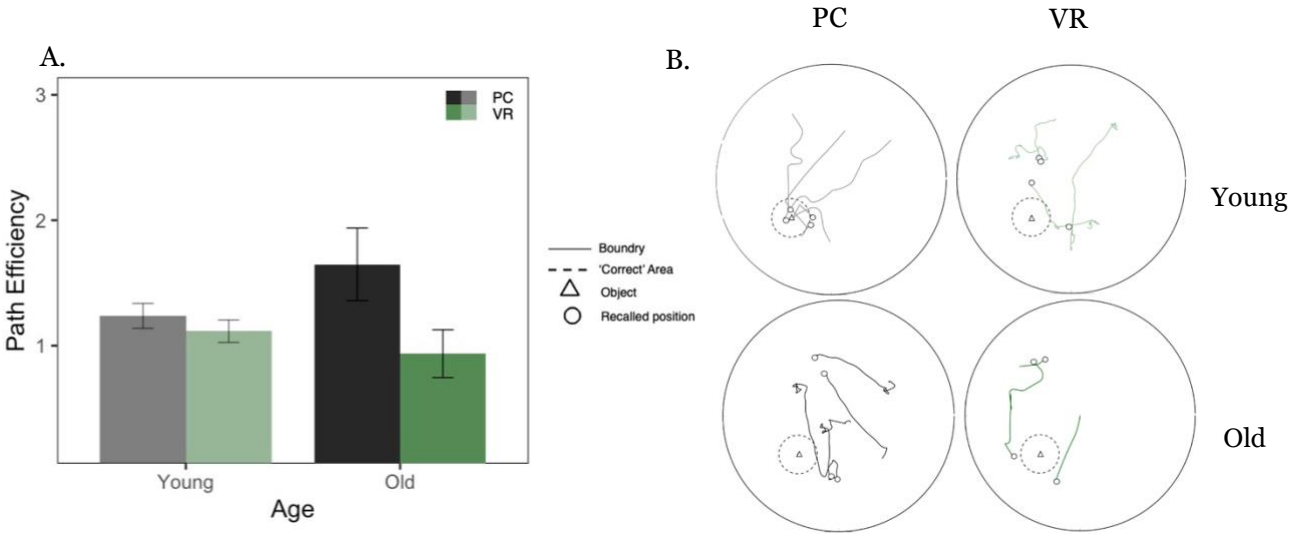

Figure 3.9. A. Average path efficiencies across the three objects and retrieval blocks for old participants on the left and young participants on the right, and for both experimental devices. The error bars represent the standard error of the mean. B. Example traces illustrating the trajectories of one young (top) and one elderly (bottom) participant navigating in the environment towards the same target location for both modalities, PC (left) and VR (right). Each line represents their trajectory during one of the four retrieval blocks. The triangle represents the target object, whereases the circle represents the participant's response, meaning where they remembered the target object was. The correct area represents the circle with a 1vm radius around the target location. Participants' responses are considered correct if they are within that circle.

3.2.3 Discussion

This study compared navigational performance and memory of two age groups on two devices using an identical task, with the aim of identifying the optimal means to acquire these measures from an older population. It was expected that the overall performance of young adults would be better compared to the elderly group, and that older adults would perform better in VR compared to the PC.

In the interest of completeness, statistical analyses were performed, and the results are presented in the Results section. However, during implementation, several experimental limitations were noted, leading to early termination of the study. Accordingly, the outcomes of this study should only be interpreted in relation to this cohort and should not be the basis for any further generalisation.

Approximately 40% of older adults who took part in this study complained of nausea, headaches and disorientation when performing the immersive VR version of the task and withdrew from the experiment. This is in line with reported increased cybersickness susceptibility for older compared to younger adults (Arns & Cerney, 2005). Cybersickness typically occurs when sensory input in the real world does not match the task experience. Several causes may have contributed to this issue such as age, or previous experience, hardware characteristics, or task design, including the smoothness of control and the predictability of events (Diersch & Wolbers, 2019; Renkewitz & Alexander, 2007). The hardware used for the immersive VR experience also had some specific limitations which may have compromised the immersive experience. Mounting of the VR device left two gaps on either side of the headset, which could potentially disrupt the immersive experience, as they acted as avenues for additional light and confounding visual stimuli. For this reason, they were covered using opaque, grey duct tape which blocked the light. However, for the tape not to stick to participants' skin, the gaps were not always entirely covered, and several participants mentioned that they were aware of their location in the testing room. Therefore, these gaps were a likely source of confusing visual input, which disrupted the immersive experience and increased the likelihood of cybersickness. Intrusion of external stimulation into the immersive display may have caused additional confusion and disorientation. Additionally, to achieve stereoscopic vision in the VR version of the task, participants had to adjust the lenses of the headset themselves to fit their physiognomy. There was no way for the researcher to verify that 3D vision was achieved and that participants did not rely on blurry or distorted visual input that could impact performance.

Second, the objects participants searched for differed between the two devices, but the environment remained identical. This may have introduced a source of interference between the two versions of the task. It is possible that, on the second testing device, object-location associations from the same environment on the first testing device caused proactive interference. This theory was reinforced by the swap measure presented, showing that participants retrieved locations corresponding to objects previously encoded in the first

version they performed in over 15% of the trials for old participants and approximately 10% of trails for young participants, which likely also increased their distance errors. This effect of this interference was more pronounced in older individuals whose associative abilities are already reduced. For this reason, a measure to prevent this type of interference could be introducing changes and variations of features in the virtual environment, including different distal cues and textures.

Considering all these limitations, it was difficult to separate the effects of ageing and of different levels of immersion from the impact of disruptive conditions. Undoubtably, these limitations contributed to the low accuracies and large distance errors measured from both age groups, on both devices. Previous studies using similar task designs and adaptations of a virtual water maze showed better participant tolerance and performance (e.g., Diersch & Wolbers, 2019; Harris & Wolbers, 2012; Harris, Wiener, & Wolbers, 2012). The main difference was the hardware used to achieve the immersive experience in VR, which was a great source of limitations in this case. Lastly, due to the high withdrawal rate, the study was terminated early and the sample size available for analysis was very small. Therefore, the results discussed below are not representative of the general population. Nevertheless, these findings and limitations provided important lessons that can inform future studies and contribute to optimisation of spatial navigation and memory measures in VR.

In line with expectations, older adults showed lower performance throughout the task, on both devices, compared to the younger group, even when controlling for differences in gaming experience. Their ability to retrieve and navigate to the target objects' locations was diminished both during practice trials, when they received feedback after each response, and during retrieval. What is more, their lower performance was also reflected in the accuracy measures recorded in the retrieval trials, where young adults reached the target location significantly more frequently in comparison. These findings are consistent with previous literature revealing the effects of ageing both on navigational abilities, as well as on the accuracy of retrieving object locations.

The task imposed an allocentric approach to navigation by placing participants in a different location at the start of each trial. Several studies previously emphasised the significant spatial memory impairment of older adults using an allocentric frame for navigation, compared to more preserved abilities in egocentric tasks (Colombo et al., 2017). These differences could be a consequence of older adults' difficulty to create and use cognitive maps of the external environment, coupled with decreased hippocampal function (Head & Isom, 2010). Second, older compared to younger adults have been shown to rely more on proximal rather than distal cues, such as landmarks (Schuck et al., 2013). However, only distal cues surrounding the arena were available in the task, which could have played a role in their lower precisions and accuracies. Lastly, although the two groups showed comparable results on the ACE-III, a standard neuropsychological test of cognition including a visuospatial component, it has been established that older adults tend to experience declines in visuospatial memory, specifically in their ability to remember objects' location in an environment. In this case, the paper-based test might not have been sensitive enough to detect these changes, which only became evident when additional cognitive demands such as navigation were included.

Measuring distance error across the four feedback blocks yielded no significant results for either of the two groups and devices. Neither young nor elderly participants showed any significant improvement throughout the blocks where they received feedback after each response. Considering that participants had completed three encoding blocks prior to this phase, this could suggest that learning was achieved during the encoding phase and that the feedback trials were not additionally helpful. Alternatively, the first feedback block could have achieved significant improvement post-encoding, but no additional learning was achieved subsequently. Future follow-up studies should consider training participants to a set criterion during the encoding task to clearly separate the effects of ageing on retrieval.

Interestingly, comparing the effects of increased immersion on the two age groups' performance yielded dichotomous results. On one hand, during practice, young participants

did not differ in their errors between the two devices, whereas during retrieval their distance errors were significantly lower on the PC. These findings are in accordance with previous research investigating navigation and spatial memory using both devices that associated the PC with better performance for young adults (Sousa Santos et al., 2009). Most young participants also reported that they spent several hours a day on the PC and multiple hours a week playing video games, whereas using the immersive VR device was a novel experience. Previous studies found that skills acquired through playing video games do not transfer from PC devices where navigation is achieved by using a joystick to immersive VR tasks (Richardson, Powers, & Bousquet, 2011). On the other hand, elderly participants had significantly smaller errors in VR during the practice blocks, whereas their retrieval performance did not differ between the two devices. One possible explanation for these results stems from the lack of familiarity of the older group with both devices used to perform the task. The fact that the VR experience was more intuitive, resembling real life navigation, and did not involve using any hardware, might have allowed participants to adapt to the task requirements faster and focus on their performance. What is more, studies have showed that older adults tend to rely more on body movement and self-motions cues available only in VR, compared to younger groups who use environmental cues, such as boundaries and distal cues, equally (Bates & Wolbers, 2014). Instead, learning to use a joystick for the PC version of the task could have contributed to older participants' cognitive overload. Alternatively, using the VR device had several limitations that caused multiple participants to withdraw from the study. These limitations could have also cancelled the benefits observed in the practice phase, after a longer exposure for those who completed the study. Furthermore, participants were present "inside" a virtual environment with higher perceptual stimulation (Richards & Taylor, 2015). The likelihood that increased immersion is a distracting factor during learning has been explored and found to distract participants from the target content (Parong & Mayer, 2018; Richards & Taylor, 2015)

Movement control during the task was different across the two devices (teleportation and free real-world movements in VR vs. walking using a joystick on the PC). For this reason,

they are not fully comparable in terms of distance travelled and response times. In this case, path efficiency was used as a measure of participants' engagement with the task, rather than as a measure of performance. No significant differences were found between the two groups or the two devices. On the contrary, previous research showed that older adults tend to walk longer distances in virtual environments compared to young participants. Although the results show a trend of higher path efficiency on the PC for old adults, their level of exploration in VR was comparable to that of young adults. Considering their low performance, these results could reflect their low engagement with the task, which was determined by the limitations discussed. When examining individual trajectories of participants from both groups, these point to the same conclusion, which is also in accordance with the researcher's observations during data collection. Furthermore, participants' lack of engagement could also be caused by increased levels of stress and anxiety. Analysing the process for older adults being introduced to technology, Barnard et al. (2013) found that both the novelty of the experience and their eagerness to perform well and make a good impression in front of the researcher can significantly elevate stress levels and anxiety in order adults, which can impact performance (Barnard et al., 2013).

Overall, this study does not provide a definitive answer for the optimal means to measure spatial memory and navigational abilities of older adults. The results indicate that PC navigation tasks might be a sufficiently reliable method for this purpose. However, the highlighted limitations of this study cast doubt on their generalisability. Therefore, the most important takeaway message consisted of suggestions for how future studies could address these challenges and improve testing of older adults using appropriate VR technologies and improved task designs. Only then will this comparison between devices will yield reliable conclusions.

First, a different VR device should be used to achieve the immersive experience. Although the price and wireless characteristics made Google Tango an accessible option, the downsides overweighed the benefits. Since data collection in 2017, technology has improved

significantly and now there are several options that do not require participants to adjust the lenses to achieve the 3D experience and that block any external visual input that could disrupt the immersive effect. Second, when designing a performance-matched task to be used on both devices, interference must be reduced. Future studies should consider using a variety of environments, with different cue and textures for the context. This way, participants' errors would likely reflect their mnemonic and navigational abilities.

Lastly, some of the limitations presented earlier stem from participants' lack of familiarity with the technology used in this experiment. In the future, this difficulty might be alleviated as digital devices become more and more incorporated in everyday life. In the meantime, future research could consider several measures to guarantee that navigational data collected from older adults are not confounded by their restricted understanding of and suboptimal interaction with the devices. Sufficient training should be provided for participants to become accustomed to using the hardware necessary. Schellenbach et al. (2010) found that when both young and elderly participants practiced walking on a treadmill while immersed in a virtual environment for 20 minutes, they were able to display stable walking patterns in during the task (Schellenbach, Lövdén, Verrel, Krüger, & Lindenberger, 2010). This way, not having to focus on the correct use of technology may free up cognitive resources required to perform and engage with the task to the best of their abilities. Diersch and Wolbers (2019) also suggest that introducing devices and task instructions step by step prior to the start of the experiment would facilitate familiarisation and reduce participants' stress levels (Diersch & Wolbers, 2019). Another important measure to consider is an evaluation of participants' cybersickness susceptibility prior to the start of the experiment, which can be achieved using the Simulation Sickness Questionnaire (Kennedy & Stanney, 1997). Setting an inclusion threshold score would help to drastically reduce withdrawal rates.

Impaired spatial memory and navigation abilities are some of the earliest indicators of a progression from healthy aging to Alzheimer's Dementia and therefore, when tested using optimal methods, could become useful markers. Although this study did not shed light on the

best means to measure these functions, it provided important lessons for designing future tasks that informed the second study presented in this Chapter.

3.3 Retrieving spatial memories of different timescales in ageing

Building on the previous study, a new PC-based navigational task was developed that enhanced the immersive experience. Like before, younger and older individuals' abilities were investigated. Their task was to learn and retrieve locations of distinct objects within different 3D environments in an allocentric frame. In addition, both measures of navigation-based WM and LTM at different delays were collected. Assuming this navigational context provided improved measures of spatial contextual learning and retrieval, I predicted a decrease in spatial memory abilities for both WM and LTM in older adults. Additionally, I anticipated that I would find a correlation between WM and LTM performances of both age groups.

3.3.1 Methods

3.3.1.1 Participants

This study was approved by the Central University Research Ethics Committee (CUREC) (research ethics project number: 08/H0606/133). All participants provided their informed consent prior to taking part in the study and were reimbursed for their time at a rate of £10/hour, as well as for their travel to the testing venue.

Thirty young participants (16 females, 14 males, age range 19-31, M = 25.1, SD = 5.6) were recruited from the community via local media and the Oxford Psychology Research (OPR) participant recruitment scheme (https://opr.sona-systems.com). Of these, six were excluded from the analysis because they were unable to perform the task above chance level (see Analysis section). The remaining twenty-four participants were included in the analysis (13 females, 11 males, age range 19-30, M = 24.25, SD = 2.4).

Thirty older participants (14 females, 16 males, ages range 62-81, *M* = 71.9, *SD* = 5.8) were recruited from the Friends of Oxford Dementia and Ageing Research platform (https://www.oxdare.ox.ac.uk/home). Two participants were excluded from the analysis, as they experienced nausea performing the task and the experiment had to be ceased. An additional seven participants were excluded from the analysis because they were unable to perform the task above chance level (see Analysis section). The remaining twenty-one participants were included in the final set of analyses (10 female, 11 male, age range 63-79, *M* = 71.26, *SD* = 2.5).

All participants were fluent in English and had normal or corrected-to-normal vision and hearing. The two groups did not differ significantly in their number of years of education.

3.3.1.2 Experimental Setup

Participants completed the experiment in a group testing room in the Department of Experimental Psychology of the University of Oxford with a capacity of 20 people, although no more than 3 people were tested at one time. Participants each sat approximately 50 cm from the monitor (Dell U2312HM Monitor, 1920 x 1080 resolution; refresh rate 60 Hz). To navigate through the task environments, participants used the mouse and WASD keys of the keyboard. The mouse was used to change the direction of the gaze, whereas the keyboard was used to move forward (W), backward (S), to the right (D) and to the left (A).

3.3.1.3 Protocol

Participants performed the study in two sessions, completed over successive days. Two experimental studies were completed over the two sessions, a navigation-based spatial memory study and a retro-cueing study. Only the spatial memory study is discussed in this chapter. The other study is discussed in Chapter 2.

On the first day, participants received instructions about the two studies to complete. They were given a chance to familiarise themselves with the apparatus and to train on the tasks. They then completed the first experimental testing session for each study. In addition,

participants completed an online set of questionnaires including demographic and descriptive questionnaires, and the Pittsburgh Sleep Quality Index. On the second day, participants completed the second experimental session for each of the two studies. The order in which tasks were performed was counterbalanced for both testing days.

For the navigation study being considered in this Chapter, the first testing day started with an introduction from the researcher about the general purpose of the study and about the hardware participants were asked to use throughout the task. Next, participants performed a practice session to ensure they were comfortable using the mouse and keyboard to navigate. If they were not able to navigate using the mouse and keyboard after 10 minutes of practice, the researcher offered to operate the hardware following the participants verbal instructions. This was necessary for four of the twenty-one elderly participants, and none of the young ones. In this case, the researcher instructed the participants to trace the desired path with their finger on the monitor during navigation, while offering verbal cues to describe the desired trajectory at all times (e.g., “go forward”, “stop”, “turn left/right”, “turn around”). Following the practice session, participants completed the first experimental session of this study. This consisted of two testing blocks, separated by a 20-minute break. During the break, participants completed a set of online questionnaires. Lastly, the second day of testing included the second experimental session.

3.3.1.4 Behavioural Stimuli

During the task, participants encoded and remembered the location of ten everyday objects within five different three-dimensional environments (Figure 3.9). All objects are available on free online 3D model repositories (https://free3d.com/3d-models/ and https://sketchfab.com). The objects always appeared at the ground level, with a z coordinate of 0. They were conspicuous and readily recognised. The object-device pairings were random across participants. However, object locations were predetermined for each environment and remained consistent across participants, regardless of object identity, to allow comparisons of

participants' trajectories in each environment. This also ensured that objects could not be randomly overlaid on obstacles in the environment.



Figure 3.9: Individual object stimuli used for the navigation task on each of the two testing modalities. Two objects were randomly paired with each of the five environments for each participant. The object locations were predetermined for each environment and remained consisted across participants.

Participants searched for the target objects in five different environments of different sizes and topographies: a Spanish piazza (38.41 x 56.89 vm), a dojo (19.19 x 22.86 vm), a residential neighbourhood (40 x 30 vm), an abandoned street (146.45 x 144.88 vm), and a laboratory room (25.02 x 25.04 vm) (Figure 3.10). These can also be found on free online 3D model repositories (https://free3d.com/3d-models/ and https://sketchfab.com). The order in which environments were presented during each phase of the task was randomised across participants. The virtual environments were developed to provide a first-person perspective of both indoor and outdoor scenes. They all had different layouts and contained obstacles that participants were instructed to navigate around, as they would in the real world. Additionally, participants could see a hand in front of them, that made the action of picking up the objects more realistic.



Figure 3.10: Screen captures of the five environments participants navigated through to find the target objects: an abandoned street, a dojo, a Spanish piazza, a laboratory room, and a residential neighbourhood.

3.3.1.5 Behavioural task

The task was used to quantify and compare spatial memory retrieval at different timescales in two age groups. Participants had to search for and keep in mind the location of everyday objects within five virtual environments. To start, participants were given time to explore and look for two objects in a simplified environment with no obstacles to adjust to the timings and to using the technology. Subsequently, testing was arranged into two phases: search and retrieval, which was measured at three time points and divided into Working Memory (WM), Medium-term Memory (MTM) and Long-Term Memory (LTM). These labels are used for separation of the three timespans of retrieval. However, both MTM and LTM measure participants' long-term memory performance.

On the first day, the task began with three blocks of interleaved search and WM trials. Each block consisted of five search trials, each followed by a WM trial, one for every environment. After the three blocks, participants answered a series of questionnaires during a 20-minute break from the task. Next, they completed one MTM block of five trials, one for each environment. Lastly, on the second day of testing, participants performed one LTM block

with one trial corresponding to each environment (Figure 3.11). They were not informed about the experimental timeline in advance.

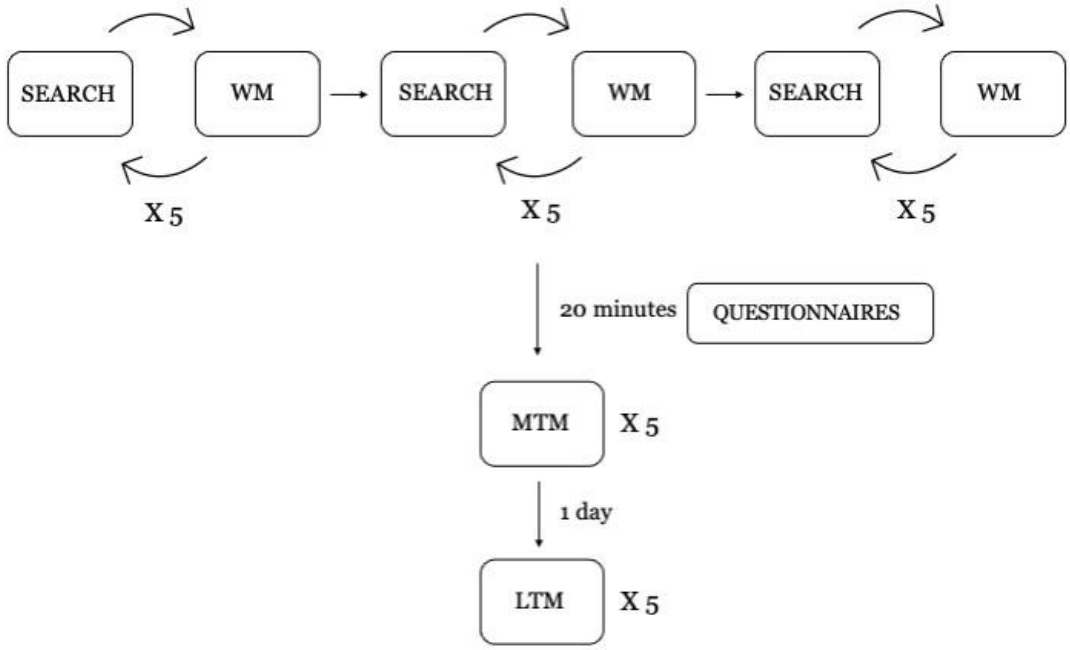

Figure 3.11: Task timeline for the two consecutive days of testing. Each block consists of the task is made of two phases: search and retrieval, which was measured at three time points and divided into Working Memory (WM), Medium-term Memory (MTM) and Long-Term Memory (LTM).

3.3.1.5.1 Search

The first phase of the task involved navigating within a three-dimensional environment represented on the computer monitor using the mouse and WASD keys on the keyboard and locating two target objects. Before the start of each trial, a set of instructions appeared on the screen along with the two objects the participants were asked to search for in the upcoming trial. The instructions were the following:

- *Please find the two objects displayed here as fast as possible.*
- *You have 60 seconds to pick them up with your hand.*
- *You just need to go to the object, and it will be automatically collected*
- *Use the mouse and WASD keys to move around.*
- *Press the spacebar to begin!*

Once participants understood the instructions, they pressed the space bar to begin each trial. They navigated around the environment and, when they identified the target objects, they walked as close to them as possible to collect them. No additional key press was necessary to respond when reaching the target location. Participants were given 60 seconds to complete each search trial. The timer appeared in the top left corner of the screen. The trials ended either when participants found both objects or when the time had elapsed, regardless of the number of objects found (Figure 3.12).

There were three search blocks in total during the task, each consisting of five trials, one for each virtual environment. For the beginning of each search trial in the same environment, participants started in different, predetermined locations which presented different perspectives within the arena to ensure allocentric navigation for all three blocks. The five environments were presented in the same order across the three blocks, but the order was randomised across participants.

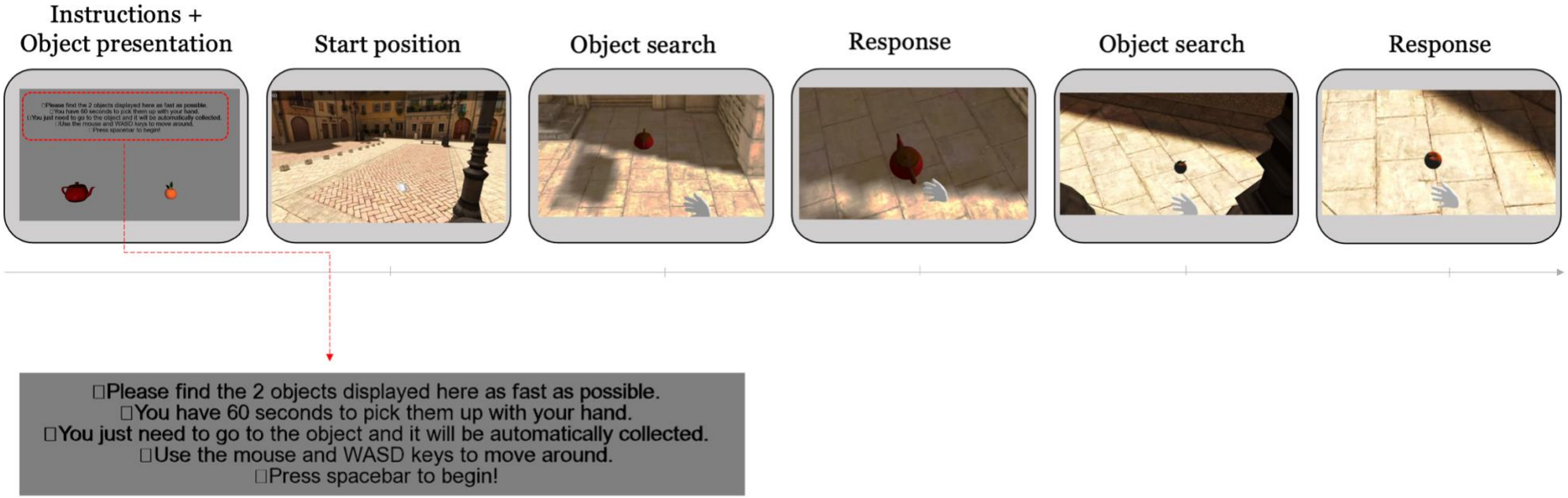

Figure 3.12: A schematic of the Search phase design. This schematic illustrates a search trial timeline in one of the five environments of the task. Participants were first shown the instructions and object identities. Next, they navigated through the environment to find the two objects within 60 seconds, and, to respond, they had to walk close to the target locations. Once they found one object, they had to continue navigating until they found the second one. Trials ended either when participants found both objects or when the allocated 60 seconds had elapsed, regardless of the number of objects found.

3.3.1.5.2 Retrieval

Participants performed retrieval trials at three different timepoints during the experiment. These were arranged into WM, MTM and LTM, according to the time difference between them and the search phase. WM retrieval trials followed each search trial, across three blocks. It is important to note that only the first WM block measured pure working memory performance. Subsequent WM trials may be influenced by longer-term learning carried over from previous blocks. MTM trials were collected after a 20-minute break for one block. LTM trials were performed the next consecutive day for one block. The stimuli and procedures followed were identical across all retrieval trials, regardless of the timepoint.

Each trial began with a set of instructions along with the array of two objects to be retrieved, corresponding to the upcoming environment. The instructions were the following:

- *Please put these objects back to where you found them.*
- *Use the mouse and WASD keys to move around.*
- *Press the "o" letter when you reach the spot where you want to put down the object.*
- *Now select the object you want to put back first by clicking on it.*

To start each trial, participants used the mouse to click on the object they wanted to place back first. Once they were back in the environment, they navigated to the remembered location of the selected object using the mouse and keyboard. To make a response when they reached the target location, they pressed the letter "o" on the keyboard. After the first object was placed in the environment, the screen with the instructions and the second object appeared. Participants had to repeat the procedure, using the mouse to select the remaining object, navigating to its remembered location and pressing "o" to respond (Figure 3.13).

There were three WM retrieval blocks, one MTM and one LTM in total during the task, each consisting of five trials, one for each virtual environment. Different start positions were predetermined for each environment for all retrieval trials, one for each return in the environment to place back a target object. These remained the same for all timepoints across

participants and offered different perspectives within the arena to ensure allocentric navigation. The five environments were presented in the same order across the three timepoints, but the order was randomised across participants.

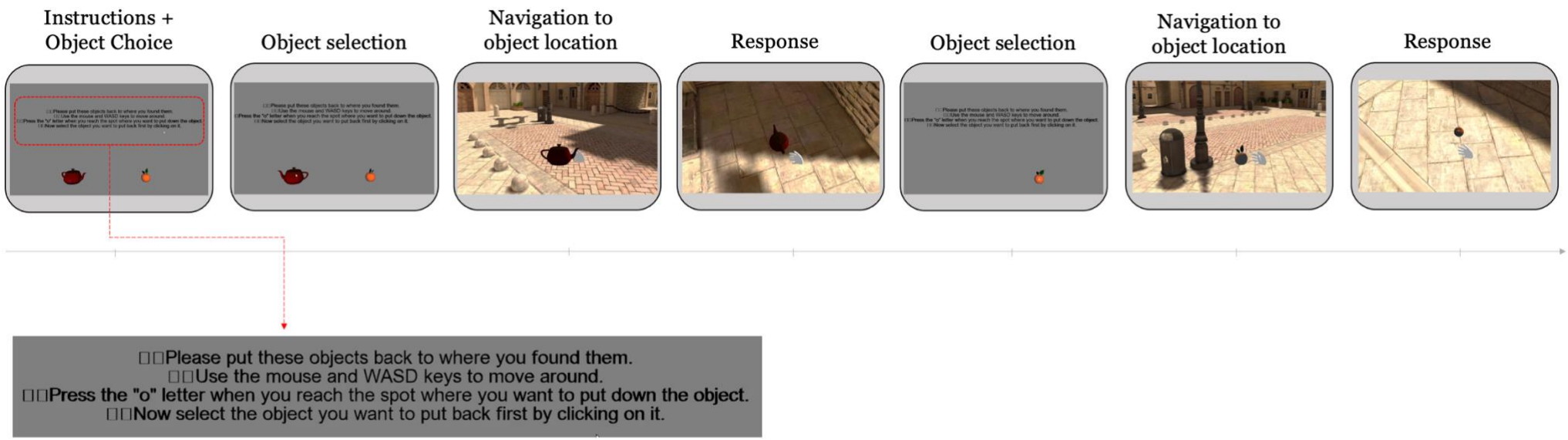

Figure 3.13: A schematic of the Retrieval phase design. This schematic illustrates a retrieval trial timeline in one of the five environments of the task. Participants were first shown the instructions and object identities previously associated with the environment. To start each trial, participants used the mouse to click on the object the wanted to place back first. Once they were back in the environment, they navigated to the remembered location of the selected object using the mouse and keyboard. To make a response when they reached the target location, they pressed the letter "o" on the keyboard. After the first object was placed in the environment, the screen with the instructions and the second object appeared. Participants had to repeat the procedure, using the mouse to select the remaining object, navigating to its remembered location and pressing "o" to respond.

3.3.1.6 Analysis

The main aim of the analyses was to compare the spatial memory performance of two age groups across multiple time points, to determine how retrieval mechanisms associated with navigation vary with age. The dependent measures computed were the proportion of unique area covered during search trials, search accuracy, distance error, response time, and proportion of trials in which object locations were erroneously swapped in an environment (swaps). During search trials, an object was considered found if the participants responded within 2 vm from the object. Similarly, retrieval trials were considered correct if participants' responses were within 2 vm from the correct target object location. This threshold was chosen after the task was piloted on 5 individuals and performed several times by the experimenter, which helped conclude that a 2 vm distance from the target during search allows participants to observe its location and context accurately even when they may not reach its exact location.

The proportion of unique area covered during search trials was calculated as the percentage of the number of unique sets of coordinates out of all coordinates composing a participants' trajectory in a specific trial. This was used as a proxy measure for perseverance and engagement during search which could also help explain their performance during search trials, as measured by accuracy and response time.

Search accuracy was calculated as the percentage of total objects found by each participant in each trial of the search phase of the experiment. If a participant's accuracy during search trials was lower than 50%, they were excluded from further analysis.

Distance error was computed as the Euclidian distance between the response position and the correct position of the respective object in virtual meters. This measure was used to analyse participants' performance in all stages of the experiment. Response time was measured from the start of each trial, when the participant was placed in the environment, until an object was found, or until the participant made a response for a remembered location and was normalised by the distance between the start and the target location.

Lastly, the proportion of swaps was calculated as the percentage of retrieval trials where participants responded within 2 vm from the location of the non-selected object associated with the same environment for the respective trial.

Data were processed and statistically analysed using the R software. Mixed-model ANOVAs were used to test the effect of age and block number on search and WM performance. Out of the three WM trials, only the first measured true working memory performance. Therefore, paired-sample t-tests were used to compare participants' working memory distance errors and response times. Additional mixed-model ANOVAs were used to test the effect of age and memory timepoint on long-term memory performance, and to investigate their performance in WM, MTM and LTM. Lastly, distance error and response-time measures were also analysed using Pearson correlations to investigate the relationship between performance at different time points. These relationships were compared between the two groups using Fisher tests. Prior to conducting these statistical tests, the assumption of homogeneity of variance was tested using Levene's test, whereas the normality of the distribution of the values was visualised using histograms, the values of skewness and kurtosis, and tested using the Shapiro-Wilk test. All assumptions were met.

3.3.2 Results

Four of the twenty-one elderly participants were unable to use the technology efficiently to complete the task. In order to check whether their performance differed from the rest of the group, the first step of the analysis consisted of comparing their mean accuracies, distance errors and response times for both phases of the task and all three timepoints. Participants' performance was comparable between the two groups (Table 3.4). Therefore, the results presented below include both groups of participants.

Table 3.4

Means and standard deviations of search accuracy and response time and distance errors and response times measured on the 1st block of WM, MTM and LTM for elderly participants who were able to use the hardware efficiently to complete the task and those who could not.

Variable	Elderly – could use hardware	Elderly – could not use hardware
Search accuracy, mean (SD)	82.6 (16)	80.3 (17.1)
Search response time, mean (SD)	34.7 (17.2)	32.7 (15.3)
WM distance error – 1st block, mean (SD)	17.3 (15.2)	18.2 (17.5)
WM response time – 1st block, mean (SD)	19.4 (12.9)	18.7 (13.7)
MTM distance error, mean (SD)	12.8 (15.6)	13.3 (12.2)
MTM response time, mean (SD)	18.2 (10.8)	17.6 (9.9)
LTM distance error, mean (SD)	14.7 (10.6)	15.2 (8.7)
LTM response time, mean (SD)	17.5 (11.9)	17.2 (10.8)

3.3.2.1 Search Results

First, search accuracy was calculated as the percentage of trials in which participants successfully found the target object. Participants who scored below 50% were excluded from further investigations. Only one elderly participant did not fulfil the criterion and was excluded from further analyses. Another measure of learning during search was response time, calculated for each block and averaged across trials.

These measures were first compared between the two age groups on the first search block, before any learning will have occurred. When comparing search accuracy, an independent samples t-test revealed a significant difference between the two groups ($t(43) = 3.89$, $p < .001$, $d = .5$), suggesting that older subjects found fewer objects on the first search block compared to young participants (Figure 3.14A). Similarly, participants' response times were compared for the first search block using an independent sample t-test. This revealed that young participants were significantly faster to respond compared to older participants ($t(43) = -5.52$, $p < .001$, $d = .4$) (Figure 3.14B).

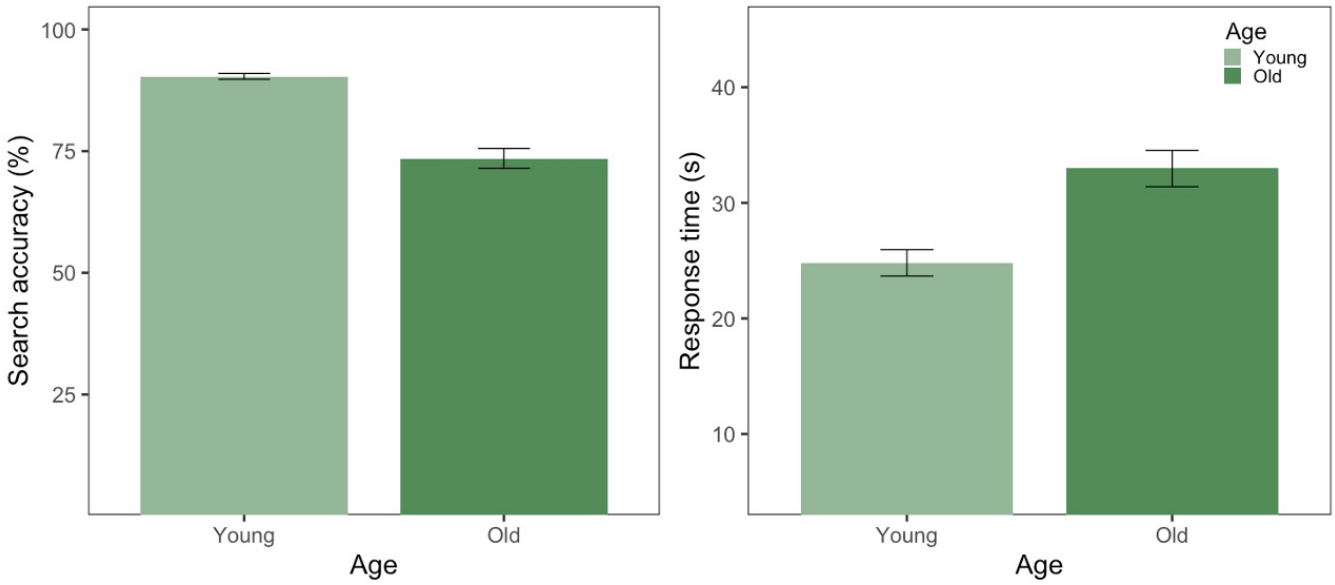

Figure 3.14 A. Average search accuracy across all objects and environments for young and elderly participants in the first search block. Young participants found significantly more objects compared to elderly individuals. The error bars represent the standard error of the mean B. Average response time across all objects and environments for elderly and young participants in the first search block, indicating that young participants responded faster compared to elderly individuals. The error bars represent the standard error of the mean.

Next, the proportion of unique area covered during search trials was compared across search trials between the two groups, using a mixed-model ANOVA with age group as the between-subject factor and block number as the within subject factor. This revealed a significant main effect of age group ($F(1,43) = 44.77, p < .001, \eta^2 = .38$), suggesting that young participants explore a larger area of the environments compared to older individuals. There was also a main effect of block number ($F(2,43) = 28.74, p < .001, \eta^2 = .27$), indicating that both age groups explored larger areas of the environments with every block. The interaction between age group and block number was not significant ($F(2,43) = 0.82, p = .42, \eta^2 = .03$).

Next, search performance was compared across all three search blocks. Examining search accuracy, a mixed-model ANOVA with age group as the between-subject factor and block number as the within-subject factor showed a significant main effect of age group ($F(1,43) = 34.97, p < .001, \eta^2 = .28$). Young participants demonstrated higher accuracies compared to elderly. There was also a main effect of block number ($F(2,43) = 26.72, p < .001,$

$\eta^2 = .17$), reflecting improvement in performance across time for both groups. Moreover, age group and block number interacted significantly ($F(2,43) = 3.26$, $p = .005$, $\eta^2 = .04$), indicating that the two groups had different patterns of learning across the three search blocks (Figure 3.15 B).

The significant interaction was investigated further by first using a one-way ANOVA for each age group. Young participants showed a significant difference between the three blocks ($F(2,22) = 6.7$, $p = .005$, $\eta^2 = .09$). Similarly, elderly participants also demonstrated a significant improvement in accuracy across the three blocks ($F(2,19) = 19.99$, $p < .001$, $\eta^2 = .24$). Additionally, the performance slopes between the first and third blocks were calculated using their difference and compared between the two age groups using an independent samples t-test. This revealed a significant difference between the slopes of the two groups ($t(43) = -2.97$, $p = .005$, $d = .2$), suggesting that old participants had a steeper learning curve compared to young participants.

Next, for response time, an ANOVA with age group as the between-subject factor and block as the within-subject factor revealed a main effect of age group ($F(1,43) = 146.88$, $p < .001$, $\eta^2 = .51$) and a main effects of block number ($F(2,43) = 32.82$, $p < .001$, $\eta^2 = .19$). There was no significant age x block interaction ($F(2,43) = 1.93$, $p = .149$, $\eta^2 = .01$) (Figure 3.15 C). These results indicate that young participants found the target objects faster compared to elderly participants, and that both groups responded faster over time.

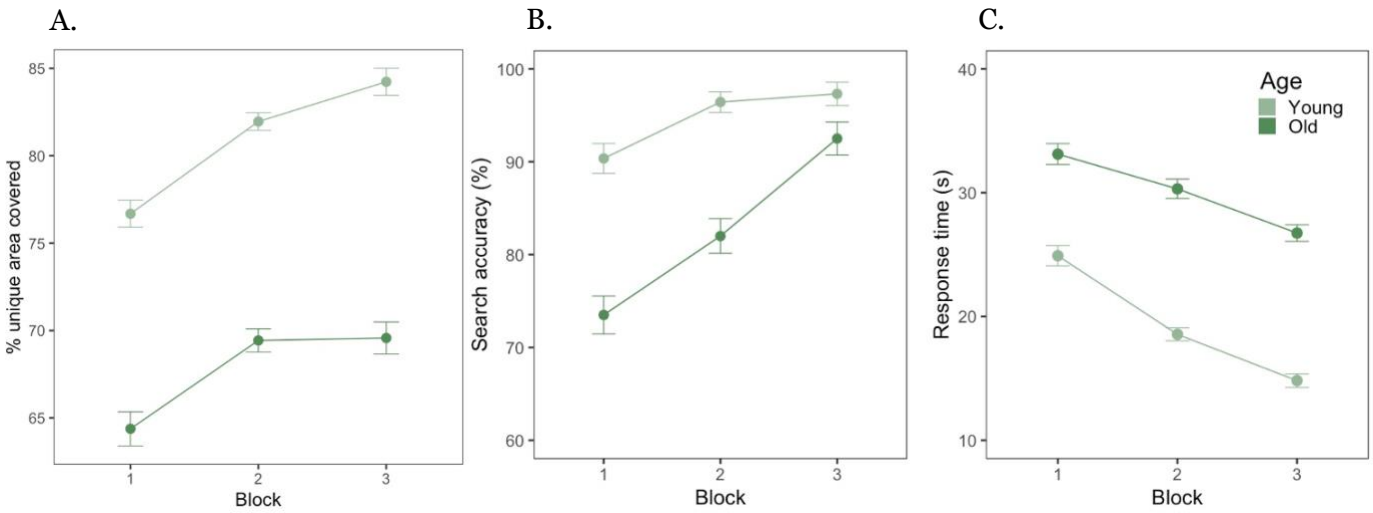

Figure 3.15 A. Average search accuracy across all objects and environments for elderly and young participants. Young participants showed greater overall accuracies compared to elderly individuals. B. Average response time across all objects and environments for elderly and young participants, indicating that young participants responded faster compared to elderly individuals, and that both age groups improved over time. The error bars represent the standard error of the mean.

3.3.2.2 Retrieval Results

3.3.2.2.1 Working Memory

The WM trials refer to the retrieval trials that followed each search. To assess participant's ability to retrieve the learned locations, distance errors and response times were calculated for each age group, averaging across all objects and environments.

To compare the true working memory retrieval abilities of the two age groups, first, their distances errors from the first WM block were investigated. An independent samples t-test revealed a significant difference between the two groups ($t(43) = -5.02$, $p < .001$, $d = .4$), suggesting that older participants made greater errors compared to young participants (Figure 3.16A). Similarly, participants' response times were compared for the first WM block using an independent sample t-test. This revealed that young participants were significantly faster to respond compared to older participants ($t(43) = -6.25$, $p < .001$, $d = .3$) (Figure 3.16B).

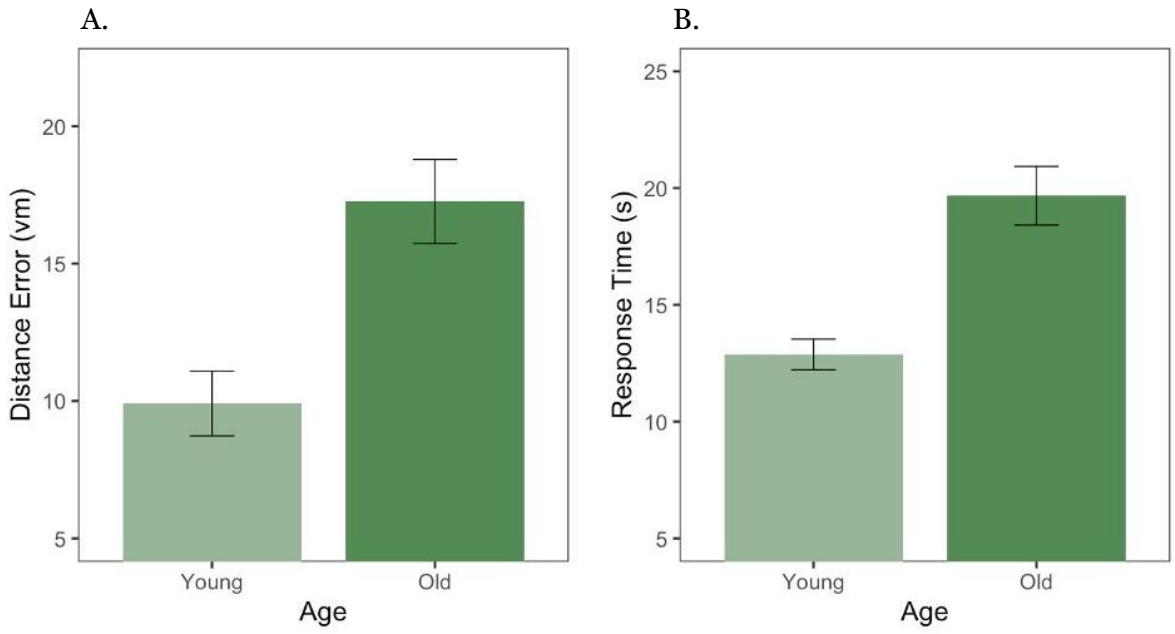

Figure 3.16 A. Average distance error across all objects and environments for young and elderly participants in the first WM block. Young participants made significantly smaller errors compared to elderly individuals. The error bars represent the standard error of the mean B. Average response time across all objects and environments for elderly and young participants in the first WM block, indicating that young participants responded faster compared to elderly individuals. The error bars represent the standard error of the mean.

Next, all three WM blocks were compared. An ANOVA with age group as the between-subject factor and block as the within-subject factor was performed. This showed a significant main effect of age group ($F(1,43) = 88.21$, $p < .001$, $\eta^2 = .4$), with young participants making significantly smaller errors compared to elderly participants. There was also a main effect of block number ($F(2,43) = 11.24$, $p < .001$, $\eta^2 = .14$), showing significant decrease in errors over the three blocks for both age groups. Lastly, there was a significant interaction between age group and block number ($F(2,43) = 3.48$, $p = .03$, $\eta^2 = .05$) (Figure 3.17 A).

The interaction was investigated further, first with a one-way ANOVA for each age group. Young participants showed a significant difference in distance errors across the three WM blocks ($F(2,22) = 7.78$, $p < .001$, $\eta^2 = .16$). Elderly participants also demonstrated a significant decrease in distance errors across the three blocks ($F(2,19) = 7.19$, $p = .001$, $\eta^2 = .21$). Next, the patterns of performance were compared using the slopes between first and second, and second and third blocks. This comparison showed that the greatest improvement

for young participants occurred between the first two blocks, whereas the improvements came later for older participants, mainly between blocks 2 and 3, although the two groups showed an overall similar amount of improvement.

Next, a mixed-model ANOVA with age group as the between-subject factor and working-memory block number as the within-subject factor comparing mean response times revealed a significant main effect of age group ($F(1,43) = 130.15$, $p < .001$, $\eta^2 = .49$), reflecting faster responses for young compared to elderly participants, as well as a main effects of block number ($F(2,43) = 4.25$, $p = .016$, $\eta^2 = .06$), indicating that both groups became faster across time. There was no interaction between age and block ($F(2,43) = .938$, $p = .39$, $\eta^2 = .01$- Figure 3.17 B).

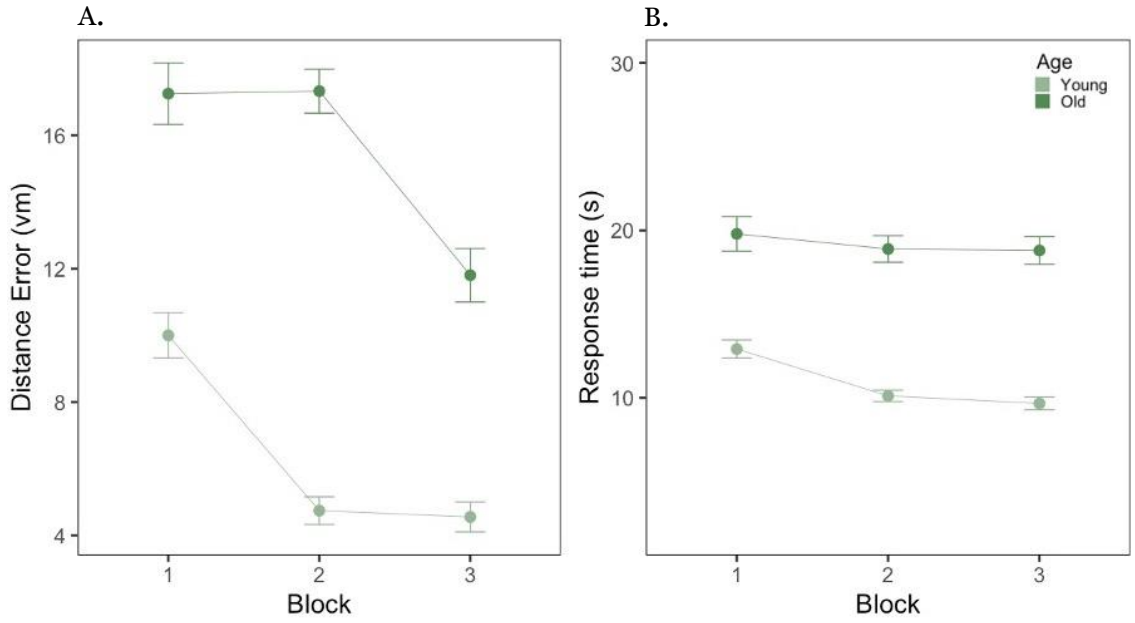

Figure 3.17 A. The plot shows the average distance error during each WM block for elderly and young participants. The error bars represent the standard error of the mean. The figure reflects the overall better performance of young compared to elderly participants, as well as their different patterns of response errors across the three blocks. B. The plot shows the average response time across all objects and environments trials for elderly and young participants. The error bars represent the standard error of the mean. This illustrates the fact that young participants were faster overall compared to elderly individuals.

3.3.2.2.2 Long-Term Memory

Participants' long-term memory was measured during the MTM and LTM retrieval trials and compared to the last WM block after all search blocks and learning was completed. To assess their ability to retrieve the learned locations, distance errors, response times and proportion of swaps were calculated for each age group, averaging across all objects and environments.

First, an ANOVA with age group as the between-subject factor and timepoint as the within-subject factor was performed to compare the two groups' distance errors. This revealed a significant main effect of age group ($F(1,43) = 32.2$, $p < .001$, $\eta^2 = .44$), with young participants making significantly smaller errors compared to elderly participants. There was also a main effect of timepoint ($F(2,43) = 4.19$, $p = .02$, $\eta^2 = .02$), showing significant decrease in performance with elapsed time for both age groups. The interaction between age and timepoint was not significant ($F(2,43) = 2.08$, $p = .14$, $\eta^2 = .01$) (Figure 3.18 A). The results remained consistent when the number of times each target object was found during search trials was included as a covariate measure. Specifically, the ANCOVA showed a significant main effect of age group ($F(1,43) = 30.1$, $p < .001$, $\eta^2 = .38$), as well as a main effect of timepoint ($F(2,43) = 3.89$, $p = .03$, $\eta^2 = .02$), Lastly, the interaction between age and timepoint remained not significant ($F(2,43) = 1.88$, $p = .18$, $\eta^2 = .01$).

Next, the source of distance errors was investigated. Swap percentages were compared using an ANOVA with age as the between-subject factor and timepoint as the within-subject factor. A significant main effect of age group ($F(1,43) = 11.24$, $p = .002$, $\eta^2 = .4$) suggested that elderly participants swapped the locations of the two objects associated with the same environment more often than young participants. Neither the main effect of timepoint ($F(2,43) = 1.43$, $p = .24$, $\eta^2 = .03$), nor the interaction between age and timepoint ($F(2,43) = 0.82$, $p = .44$, $\eta^2 = .05$) were significant (Figure 3.18 C). The results remained consistent when adjusting for the number of times each target object was found during search trials.

Lastly, response times were compared between the two groups for the three time points using an ANOVA with age as the between-subject factor and timepoint as the within-subject factor. This revealed a significant main effect of age group ($F(1,43) = 73.04$, $p < .001$, $\eta^2 = .57$), with young participants responding significantly faster compared to elderly participants. Neither the main effect of timepoint ($F(2,43) = 0.01$, $p = .91$, $\eta^2 = .01$), nor the interaction between age and timepoint ($F(2,43) = 0.3$, $p = .59$, $\eta^2 = .02$) were significant (Figure 3.18 B). The results remained consistent when adjusting for the number of times each target object was found during search trials.

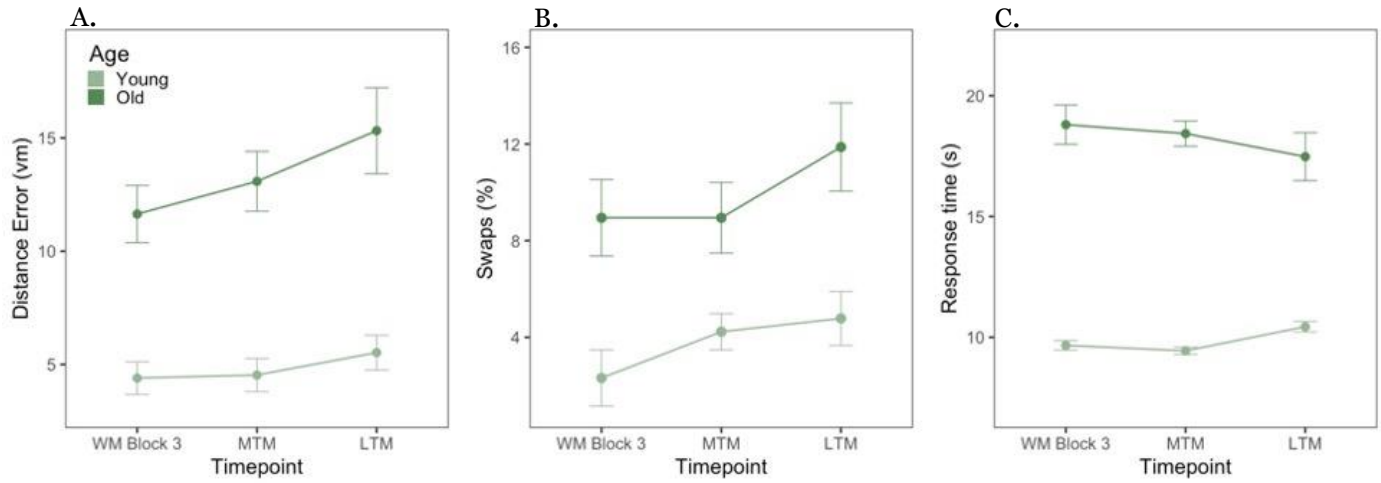

Figure 3.18 A. The plot shows the average distance error during the last WM block, MTM and LTM retrieval trials for elderly and young participants. The error bars represent the standard error of the mean. The figure reflects the overall better performance of young compared to elderly participants. B. The plot shows the average swap percentage across all objects and environments trials for elderly and young participants. The error bars represent the standard error of the mean. This illustrates the fact that young participants swapped object locations less compared to elderly individuals. C. The plot shows the average response time across all objects and environments trials for elderly and young participants. The error bars represent the standard error of the mean. This illustrates the fact that young participants were faster overall compared to elderly individuals.

3.3.2.2.3 Timepoint Comparisons

Next, to investigate participants' performance and the relationship between different memory systems, the first WM block, MTM and LTM trials were compared.

First, distance errors were calculated and averaged across objects and environments for all participants and timepoints. A mixed-model ANOVA with age group as the between-subject factor and retrieval timepoint as the within-subject factor was performed. The results revealed a significant main effect of age group ($F(1,43) = 74.08$, $p < .001$, $\eta^2 = .4$), with elderly individuals demonstrating larger errors compared to young ones. The main effect of timepoint was also significant ($F(2,43) = 10.68$, $p<.001$, $\eta^2 = .2$) and was investigated further using a one-way ANOVA for each age group. Young participants showed a significant difference between the three timepoints ($F(2,22) = 15.22$, $p < .001$, $\eta^2 = .3$). What is more, a Tukey post-hoc test revealed that young participants' distance errors decreased significantly from WM to MTM ($p < .001$) but remained consistent from MTM to LTM ($p = .68$). Elderly participants also showed significant differences in their distance errors across the three timepoints ($F(2,19) = 24.45$, $p = .03$, $\eta^2 = .2$). A Tukey post-hoc test revealed that their distance errors decreased from WM to MTM ($p = .03$), as well as between MTM and LTM ($p = .04$). The age x timepoint interaction was not significant ($F(2,43) = .6$, $p = .17$, $\eta^2 = .01$) (Figure 3.19 A). The results remained consistent when adjusting for the number of times each target object was found during search trials.

Next, the source of distance errors was investigated. Swap percentages were compared using an ANOVA with age as the between-subject factor and timepoint as the within-subject factor. A significant main effect of age group ($F(1,43) = 11.98$, $p = .001$, $\eta^2 = .47$) suggested that elderly participants swapped the locations of the two objects associated with the same environment more often than young participants. Neither the main effect of timepoint ($F(2,43) = 1.63$, $p = .52$, $\eta^2 = .01$), nor the interaction between age and timepoint ($F(2,43) = 1.29$, $p = .28$, $\eta^2 = .01$) were significant (Figure 3.19 B).

The last variable measured to compare retrieval performance across the three timepoints was response time. Another mixed-model ANOVA was performed, with response time as the dependent variable, age group as the between-subject factor and timepoint as the within-subject factor. The results revealed significant main effects of age ($F(1,43) = 127.45$, p

< .001, η^2 = .51), young participants being faster than elderly, and a main effect of timepoint (F(2,43) = 6.67, p = .001, η^2 = .1). This effect was investigated further using a one-way ANOVA for each age group. Young participants showed a significant difference between the three timepoints (F(2,22) = 21.77, p < .001, η^2 = .4). A Tukey post-hoc test revealed that young participants became significantly faster from WM to MTM (p < .001) but remained consistent from MTM to LTM (p = .19). On the other hand, elderly participants maintained a consistent response time across the three timepoints (F(2,19) = 1.41, p = .24, η^2 = .2). The age x timepoint interaction, however, was not significant (F(2,43) = 1.02, p = .36, η^2 = .02) (Figure 3.19 C).

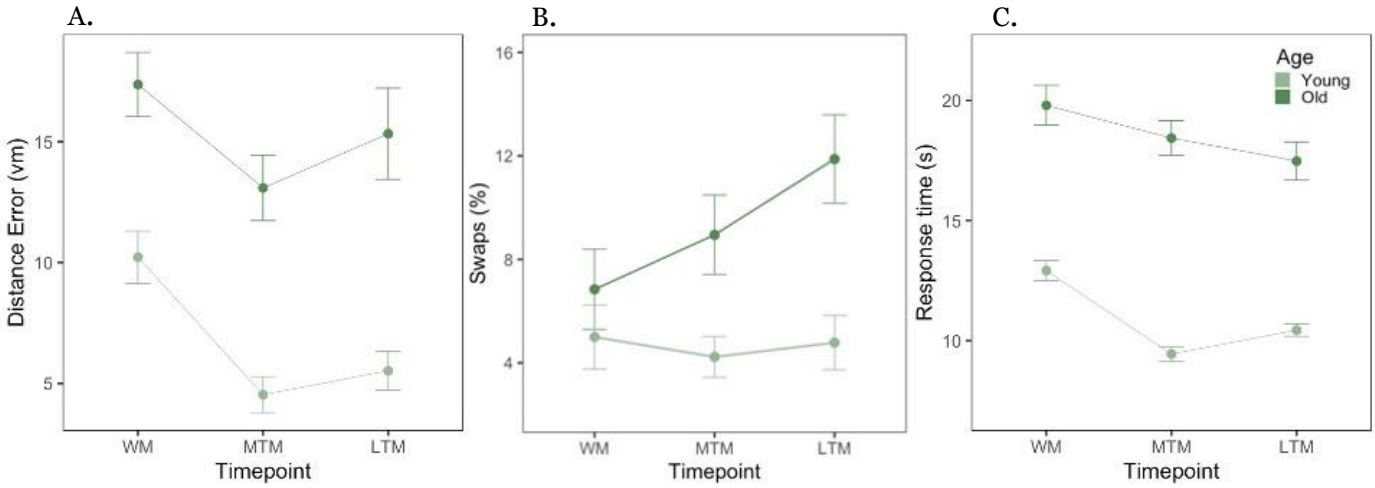

Figure 3.19 A. The plot shows the average distance error during the first WM block, MTM and LTM retrieval trials for elderly and young participants. The error bars represent the standard error of the mean. The figure reflects the overall better performance of young compared to elderly participants. B. The plot shows the average swap percentage across all objects and environments trials for elderly and young participants. The error bars represent the standard error of the mean. This illustrates the fact that young participants swapped object locations less compared to elderly individuals. C. The plot shows the average response time across all objects and environments trials for elderly and young participants. The error bars represent the standard error of the mean. This illustrates the fact that young participants were faster overall compared to elderly individuals.

3.3.2.3 Timepoint Correlations

Lastly, the relationships between participants' performance at different timepoints were investigated. For this purpose, a series of Pearson correlation tests for distance error for

all time points and age groups were conducted. The measures used for WM were collected in the first WM block.

First, the correlation between distance errors during WM and MTM was measured. This revealed that the two performances were moderately positively correlated ($r(22) = .42$, $p = .03$) for the young group, indicating that young participants who perform well in the WM stage, also perform well after a 20-minute delay, in the MTM block. On the other hand, elderly participants' distance errors in the two timepoints were not correlated ($r(19) = -.03$, $p = .44$). (Figure 3.20 A). To determine whether the relationship between memory timepoints differs with ageing, the correlation coefficients between groups were compared using a Fisher test. This conservative test did not provide evidence for a significant change in the relationship between WM and MTM performance with age ($p = .06$). Next, a strong positive correlation between young participants' MTM and LTM distance errors was revealed ($r(22) = .76$, $p < .001$), but no significant correlation for elderly participants ($r(19) = -.29$, $p = .28$) (Figure 3.20 C). This time, the Fisher test revealed a significant difference between the relationship between MTM and LTM of the two groups ($p < .001$), suggesting different levels of forgetting with ageing.

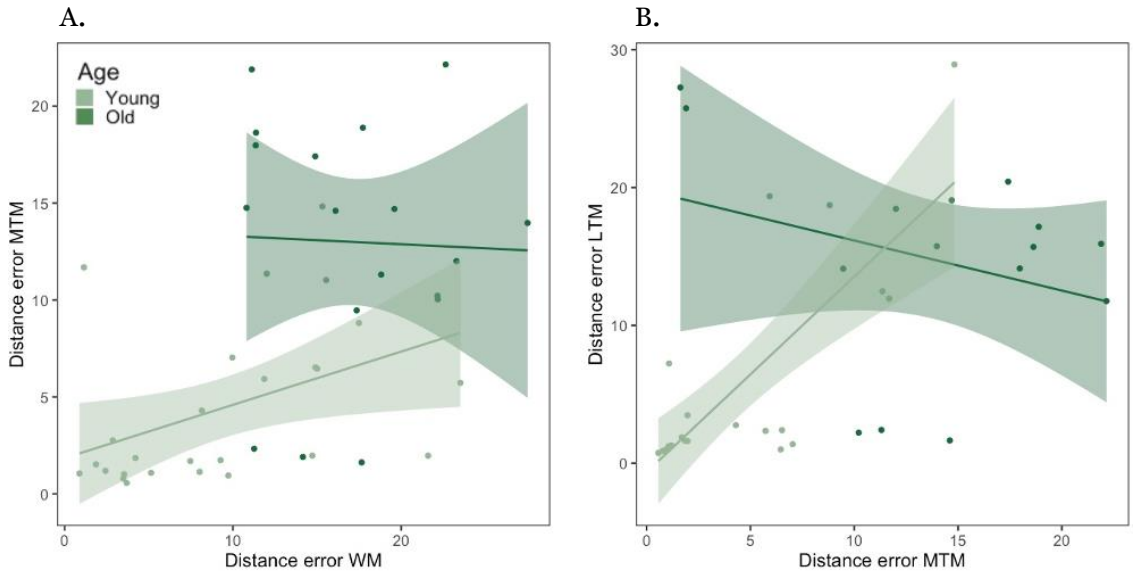

Figure 4.12. A. The plot illustrates correlations between participants' distance errors during WM and MTM for both age groups. This indicates that young participants who perform well in the

first WM block, also show low errors in MTM. B. The plot illustrates correlations between participants' distance errors in MTM and LTM trials, for both age groups. This reflects the facts that young participants' performance was positively correlated for the two timepoints.

3.3.3 Discussion

The aim of the second study was to quantify and compare spatial memory retrieval linked to navigation at different timescales in two age groups. To avoid high withdrawal rates caused by cybersickness, navigation in a virtual environment on the PC was considered appropriate for this study. Participants had to search for and keep in mind objects' locations in several virtual environments and were asked to retrieve them at three different time points. I expected to find a decrease in spatial memory abilities for both WM and LTM in older adults. Additionally, I anticipated that I would find a correlation between WM and LTM performances of both age groups.

First, unlike in the previous study presented in this chapter, both groups were able to tolerate and complete the task. Although two of the elderly participants felt discomfort in performing the task, the great majority had no problems with the procedures. Four of the elderly participants also required assistance with the hardware involved as they could not use the mouse and keyboard to navigate efficiently during the practice task. For this reason, the researcher offered to operate the hardware following the participants thorough verbal instructions to navigate through the environment. Considering earlier findings and the fact that the aim of this study was not to measure technical abilities, they were included in the analyses. Previously, Jebara et al. (2014) investigated the effect of different degrees of participation during a virtual navigation task for two age groups. Participants were either passive passengers, active passengers making all navigational decisions, drivers with no decision-making abilities, or active drivers. They found that actively participating in the decision of the itinerary led to improvements in the episodic memory of older adults, and that their performance did not differ significantly between the two active conditions, while maintaining age-related deficits (Jebara, Orriols, Zaoui, Berthoz, & Piolino, 2014).

When comparing the two age groups at all stages of the task, young adults performed better compared to the older group, in line with the first hypothesis. Older adults exhibited worse performance during both search and retrieval, at all timepoints for all variables. They were less accurate in their object search, made greater errors when localising the objects in the environments, originating from a greater proportion of swaps, and were overall slower compared to young participants. These findings are consistent with previous reports of both WM and LTM impairments of objects' locations retrieval (Korkki et al., 2018; Yoni Pertzov et al., 2015; Salvato et al., 2016a). They are also consistent with reduced allocentric navigation abilities in old age identified by previous studies (Head & Isom, 2010). Lastly, young participants' shorter response times could also be an indicator of familiarity with the technology, instead of a reflection of differences in memory abilities.

First, young and old individuals' search abilities differed in the first search block. However, this was likely due to different levels of comfort using the mouse and keyboard to navigate through the environment. This theory is supported by the fact that, by the third search block, the difference in the groups' search accuracies reduced significantly. What is more, whereas young participants' search accuracy improved gradually during each block, older adults showed a steeper learning curve after more encoding trials. These results are contrary to previous effects observed in studies using a virtual adaptation of the Morris Water Maze. The latter have shown that older adults generally present slower learning rates (e.g., Daugherty et al., 2015). Perhaps initial differences in learning rate did not stem from task difficulty, but from discomfort using the technology, which young participants were accustomed to, and elderly adapted to quickly within the three blocks.

Participants' search performance was also reflected in the interleaved WM trials which showed old participants improving significantly after more trials, whereas young individuals improved gradually in their WM retrieval. What is more, this improvement both in search performance as measured by search accuracy, and in retrieval performance as indicated by smaller distance errors, was also supported by an increase in participants' perseverance to

explore new areas of the environment as showed by larger proportions of unique locations in the environment visited, instead of revisiting the same locations. Exploring more locations of the environment enhances participants' chances to find the target objects, increasing the number of encoding episodes for those targets.

When comparing the two memory systems, the results showed that, regardless of the age group, there was a significant improvement in participants' performance from the first WM block which measured pure working memory abilities to MTM trials. Both young and elderly participants were more precise when identifying objects after a 20-minute break. This finding was in accordance with previous studies using different, non-spatial navigation tasks that have demonstrated progress in performance when retrieval was tested after a break, following multiple encoding events (Fukuda & Vogel, 2019).

However, the MTM results were also conflated with the additional encoding opportunities available earlier in the task, following the first WM block. In fact, when investigating performance on the three preceding WM retrieval trials results showed that both groups improved across blocks, showing a similar overall amount of improvement, despite young participants performing better. Additionally, different patterns of WM retrieval were observed in the two age groups. Young participants showed a steeper improvement in their distance errors from the first to the second block, unlike the older group who required an additional block and improved their retrieval after the second block. It is important to note that each WM trial was following a search trial and could represent another source of learning. Grimaldi & Karpicke (2012) demonstrated that attempting retrieval enhanced subsequent encoding and recall of the same content relative to not attempting retrieval (Grimaldi & Karpicke, 2012). The theory of retrieval as mental simulation that enhances learning was also supported by Kent & Lamberts (2008) who speculated that the relationship between encoding and retrieval results from a cognitive system that reactivates processes involved in encoding to retrieve information, which could further increase learning (Kent & Lamberts, 2008). In the current study, older adults might have benefitted from multiple exposure opportunities

more than young participants, both in the WM retrieval trials, and subsequently during MTM and LTM trials.

Additionally, comparing the first WM block with MTM and LTM retrieval performance also revealed that, despite both groups' improvement from WM to MTM, neither improve further on the second day of testing. In fact, there was significant forgetting or decrement in performance for the elderly group, whereas this was not evident for the younger group. This could indicate a subtle deficit in memory consolidation compared to young participants' whose performance remained significantly better than in the first retrieval block. Huppert and Kopelman (1989) found similar results when comparing young and old healthy adults' retrieval performance on a visuospatial task 10 minutes, 24 hours and 1 week after encoding. Their results also indicate that significant differences in forgetting rates occurred within the first 24 hours. However, this result could stem from different number of times objects were found during search trials, which could lead to fewer encoding opportunities or from unequal levels of encoding. The first option was addressed and excluded as a possibility by adding the number of times a target object was found as a covariate and this finding remained. Future studies could consider the second possibility which could be resolved by training participants to an established criterion before measuring their long-term retrieval abilities.

Interestingly, older participants were also found to make more swap errors compared to young participants. Pertzov et al. (2015) revealed a similar finding using a WM task and a similar method of calculating this measure. However, that result was explained by a deficit in object identity retrieval for older compared to young individuals. In the current study, objects were presented on the screen and participants did not have to also recall their identity. Instead, this spatial memory task might be more hippocampal-dependent, and therefore the measures could be more sensitive to age-related changes. What is more, the proportion of swaps remained consistent in the elderly group and therefore is unlikely to explain the forgetting between MTM and LTM.

Next, as hypothesised, when examining the relationship between the two memory systems, young participants' MTM performance correlated both with their WM and their LTM performance. On the other hand, analysis of the older group did not yield any significant correlations, contradicting the original predictions. Regardless of the post-encoding delay, memories for object-location associations, are thought to rely on the MTL, and more specifically, on the hippocampus (Kolarik, Baer, Shahlaie, Yonelinas, & Ekstrom, 2018; Zokaei et al., 2019a). However, WM is also known to rely on the prefrontal cortex for encoding, maintenance and manipulation of the information (D'Esposito et al., 2000). This could be a possible explanation, assuming the different rate of impairment of the two structures could lead to an erosion in the strength of correlations in old age. Although the correlations in older participants were not significant, this could also stem from lower statistical power. Additionally, the relationships between WM and MTM were not found to differ between groups, indicating the pattern of use with remains consistent with ageing. However, the relationship within long-term memory tested a different timepoints seemed to change with time, reinforcing the finding that elderly participants have increased forgetting tendencies.

One limitation of this study was the low number of trials available for analysis of each condition. Future studies should consider increasing the number of retrieval trials, which would allow for additional statistical analyses. To allow for a clear separation of the effects of ageing on spatial memory from encoding deficits, follow-up studies should also consider training both groups to a set criterion prior to probing their retrieval abilities. This could be achieved by increasing the number of encoding trials. Moreover, there may have also been an effect of the rate at which different groups became familiarised with the procedures. Therefore, it may be useful for future studies to introduce additional WM practice trials and then introduce new environments for accurate testing of pure WM. Additionally, all WM trials except for the first one could be eliminated, as they were only used to measure learning, but not for memory systems' comparisons.

What is more, to analyse navigational abilities at different timepoints separately from participants' spatial memory of objects-location associations, an additional phase could be added to the task. This would involve asking participants to retrieve previously encoded objects' locations statically, without being to able to advance, but only to rotate, receiving a 360 degrees view of the scene where they could mark the target location. An allocentric perspective could be ensured by placing them in a new position at the start of each trial and asking them to click on the remembered location. This variation would contribute to the findings proposed by earlier studies that showed different levels of sensitivity of navigation abilities and object-location association measures as assessments of older individuals and those predisposed to developing Alzheimer's Disease (Coughlan et al., 2019; Gellersen, Coughlan, Hornberger, & Simons, 2021).

Finally, building on these findings, this task could be used to test groups at risk of developing Alzheimer's Disease or cohorts of patients with established hippocampal damage, which could reveal different memory patterns of the same content characteristic to each cohort. Some of the advantages include the fact that this approach enables measuring of memory abilities formed from natural, common navigational experience, using sensitive measures that can also provide insight into the source of errors (swaps).

To my knowledge, this is the first human study to compare navigation-based spatial associative memories at different timepoints in two age groups and to test their relationship, using sensitive continuous report measures within the same task. The findings suggest that, besides the impairing effect of age on both working and long-term memory, older participants also show considerably more forgetting that is probably not related to an increased swap rate. Future studies should further explore these divergent patters, as they could become markers of unhealthy ageing.

4. Spatial memory and navigation in limbic encephalitis

Abstract

Studies of healthy ageing facilitate our insights into the natural development of the patterns of WM and LTM use with time but are limited in how much they can reveal about underlying mechanisms. For this reason, individuals diagnosed with limbic encephalitis (LE) provide a unique opportunity to investigate the two memory systems as they present with focal MTL damage. The study described in this chapter used a navigation-based spatial memory task to measure and compare WM and LTM in equivalent ways in two cohorts of elderly individuals, one healthy and one with LE. The results showed that, despite participants with LE being slower in their WM retrieval compared to healthy adults, they remembered the objects' locations with similar precision both in WM and LTM. However, in the context of the ongoing COVID-19 pandemic, the results remain inconclusive because of the small number of participants and low statistical power and should not be generalised to a larger LE population. Future studies should certainly further explore the methods and analyses presented, using a larger sample size, as this could provide invaluable information about the different patterns of use of the two memory systems in ageing and disease.

4.1 Introduction

Returning to the dichotomy between working memory (WM) and long-term memory (LTM) proposed earlier in the thesis, research has shown consistently that both memory systems show impairment with ageing (Korkki et al., 2018; Yoni Pertzov et al., 2015). However, the relationship and potential dissociations between the two memory systems and their underlying mechanisms have not received much attention so far.

Behavioural ageing studies enable an understanding of the natural progression of the patterns of WM and LTM use but are constrained in how much they can elucidate the

mechanisms' underlying changes. For that reason, studies including a clinical cohort, with documented and detailed impairments, become an invaluable source of information about the interdependence of the core mechanisms of the two memory systems. For example, research has consistently demonstrated that, despite not being entirely coextensive, both WM and LTM rely on medial temporal lobe (MTL) and hippocampal integrity for normal functioning for normal encoding, maintenance, and retrieval of spatial and contextual information.

In fact, it was Scoville and Milner's influential patient study in 1957 that started the conversation about the role of the medial temporal lobe (MTL) and the hippocampus in memory (Scoville & Milner, 1957). Their seminal findings suggested that patients with bilateral MTL damage present with anterograde amnesia, meaning that newly acquired information, such as where they had parked their car, was forgotten 'as fast as it occurred'. Back then, these findings led researchers to conclude that short-term memory (later coined WM) was spared, and that only LTM was affected by MTL damage (Scoville & Milner, 1957).

Later, Cohen and Eichenbaum (1993) advanced the idea that, in fact, the MTL and hippocampus support declarative memory by providing an associative processing mechanism across different tasks and domains (Cohen & Eichenbaum, 1993). Numerous subsequent studies supported their theory (Cabeza et al., 2008; Hannula & Ranganath, 2008; Hannula, Tranel, & Cohen, 2006; Olson et al., 2006; Piekema, Kessels, Mars, Petersson, & Fernández, 2006; Ranganath & D'Esposito, 2001). Imaging studies with both healthy participants and individuals with MTL damage demonstrated that the MTL is activated in maintaining relational information in memory, particularly when associations involved a spatial component (Hannula et al., 2006; Olson et al., 2006; Piekema et al., 2006). A possible reason for this specificity might be the role the hippocampus plays in spatial memory and navigation, as found by O'Keefe and Dostrovsky (1971) (J. O'Keefe & Dostrovsky, 1971).

Lastly, imaging studies also investigated and compared the neural correlates of the two memory systems. LTM and WM have typically been probed using separate and distinct tasks. Findings showed that both systems recruit the MTL and hippocampus, confirming that

relational operations conducted by these structures apply to both WM and LTM (e.g., Cabeza, Dolcos, Graham, & Nyberg, 2002).

The current study was designed to shed light on the patterns of spatial WM and LTM impairment that result from MTL damage, using equivalent measures for both functions. It capitalised on an unusual clinical cohort with autoimmune limbic encephalitis (LE), which is associated with focal MTL damage.

4.1.1 Limbic Encephalitis

LE was first described in 1960 by Brierley and colleagues as a series of three clinical cases (Brierley et al., 1960). Significant progress has been achieved since then in the understanding of symptoms and comorbidities of the disease. However, the pathogenesis remains elusive due to the heterogeneity of symptoms. The most prevalent hypothesis states that the immunological response, in the form of antibodies, is incorrectly directed to limbic system antigens (Anderson & Barber, 2008).

The term "limbic encephalitis" was coined in 1968 by Corsellis et al, when they described their observations of bronchial carcinoma accompanied by memory loss and dementia. This study was the first to establish an association between LE and cancer. Initially LE was thought to be a rare complication of cancer (Corsellis, Goldberg, & Norton, 1968). It is now known to be predominantly a disease triggered by an altered immune response to cancer cells, which also targets cells in the medial temporal lobe with similar antigens (Anderson & Barber, 2008). However, it can also occur in the absence of malignancy.

The leading sign of LE in the acute phase is a severe anterograde amnesia, frequently accompanied by behavioural and psychiatric symptoms such as anxiety, depression, irritability, personality changes, confusion, hallucinations, and complex partial and secondary generalised seizures. These symptoms usually develop over the course of weeks or months (Anderson & Barber, 2008; Pastuszak et al., 2017). Nevertheless, LE can have heterogenous

presentations, which, in turn, can lead to delayed diagnosis and varied progression of the disease. The improvements in neuroimaging and identification of antineuronal antibodies in patients with LE have facilitated earlier identification of the disease (Anderson & Barber, 2008).

For diagnosis, the criteria established by Gultekin et al. (2000) were widely used until 2016. They have since been updated by Graus et al. (2016), and diagnosis is made once all the following criteria have been met (Graus et al., 2016; Gultekin, Rosenfeld, Voltz, & Eichen, 2000):

i) Sub-acute onset of memory deficits, seizures, or psychiatric manifestations suggesting involvement of the limbic system

ii) Bilateral brain abnormalities, typically manifesting as hyperintensities, on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes

iii) At least one of the following:

- CSF pleocytosis (white blood cell count of more than five cells/mm^3)
- EEG showing epileptic or slow-wave activity in the temporal lobes

iv) Justified exclusion of alternative causes

Recently, clinicians established an approach to the investigation and acute management of LE relying on research findings. Obtaining MRI of the brain and inspecting the CSF represent the first step, as medial temporal lobe abnormalities observed in the MRI scans are useful biomarkers to confirm an LE diagnosis. Patients typically present with hyperintense signal and mild swelling of the medial temporal lobes in their T2-weighted and FLAIR MRI sequences, which may eventually be replaced by medial temporal lobe atrophy (Ances & Vitaliani, 2005) (Figure 4.1). When additionally acquired, positron-emission tomography (PET) sometimes reveals hypermetabolism in the medial temporal lobes, even when MRI is normal. Lymphocytic pleocytosis, increased protein concentrations, and oligoclonal bands in the CSF are some of the typical markers for an LE diagnosis. The second step is searching for malignancy and identifying antineuronal antibodies. Several of the antibody tests necessary are not available in commercial laboratories, and CSF and serum

samples must be sent to a research laboratory, which delays the diagnostic process (Graus et al., 2016). Given the rapid progression of the disease, patients are typically recommended to begin treatment with immunoglobulin or corticosteroids before receiving the results of those tests (Ances & Vitaliani, 2005; A Vincent et al., 2004). An EEG is usually part of the diagnosis process as well, showing focal or generalised slow wave abnormalities, and epileptiform activity, electrographic seizures, or periodic lateralised epileptiform discharges in the temporal regions (Graus et al., 2016).

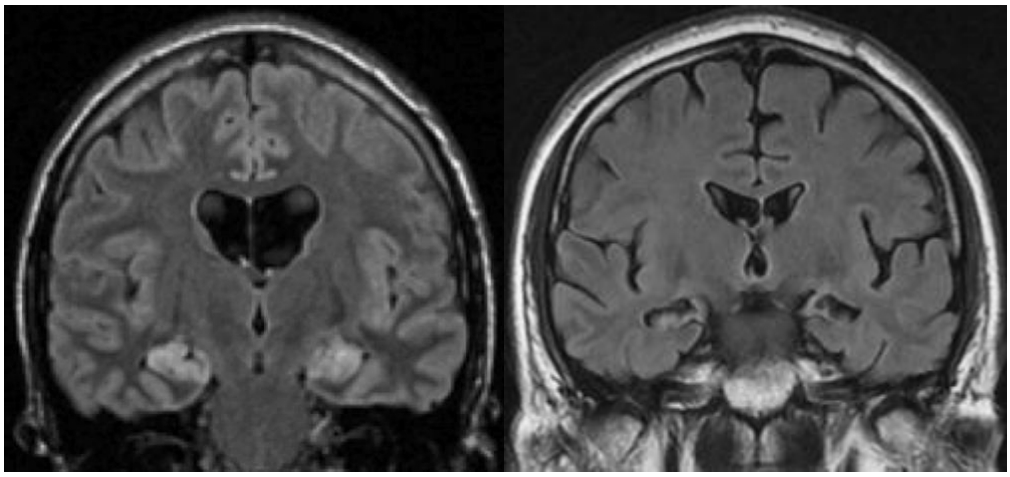

Figure 4.1. Coronal sections of T2-weighted MRI of a participant diagnosed with LE in the acute phase (left), displaying inflammation in the medial temporal lobe and in the post-acute phase (right) displaying atrophy in the medial temporal lobe.

LE associated with antibodies to the voltage-gated potassium channel complex (VGKC) is one of the most common forms of the disease. VGKCs are important for restoring the resting-state ion concentration in the cells after an action potential, and are located in the membranes of neurons both in the central and peripheral nervous systems (Vincent, Bien, Irani, & Waters, 2011). The antibodies target proteins associated with the VGKC, identified in extracts of mammalian cortical neuronal membranes: leucine-rich glioma-inactivated1 (LGI1) and contactin-associated protein-like 2 (Caspr2) (van Sonderen, Schreurs, Wirtz, Sillevis Smitt, & Titulaer, 2016). The antibodies are detected using binding assays performed on cells engineered to express the target antigens. Research suggests that VGKC LE predominantly

targets the medial temporal lobe (MTL), particularly the hippocampus (Butler et al., 2014; van Sonderen et al., 2016).

Overall, VGKC LE is characterized by sub-acute memory loss, confusion, agitation, and other psychiatric features developing over several days or weeks. Both subtle partial and generalised tonic clonic mid-temporal lobe seizures are typically present. T2 or FLAIR high signal is present in the mesial temporal lobes, either unilaterally or bilaterally, in most patients. The amygdala is also sometimes affected. EEG usually shows interictal epileptiform activity or slowing over antero-temporal or mid-temporal and sometimes also over frontal regions (Vincent et al., 2004; Vincent et al., 2011).

Patients usually show substantial improvement with treatment. Seizures typically respond poorly to anti-epileptic drugs, but respond well to immunotherapies such as steroids, plasma exchange, and intravenous immunoglobulins. In the post-acute phase, most symptoms subside, apart from memory deficiencies. Lastly, the T2 hyperintensities on the MRI lead to MTL atrophy in the post-acute phase of the disease (Figure 4.1) (Argyropoulos et al., 2019; Butler et al., 2014).

4.1.2 Memory Impairment in Limbic Encephalitis

Given its cardinal characteristic of anterograde amnesia, patients with LE can play a significant role in memory research seeking to identify cognitive markers of the disease presence and outcome, valuable to both to clinicians and future research. Moreover, studying this cohorts can help to elucidate the dependence of cognitive functions on the MTL, and thus help clarify the nature of the relationship between WM and LTM for the same materials.

Pertzov and colleagues (2013) previously assessed the WM abilities of LE patients. They used a visual WM memory task with a sensitive, continuous measure of report. Participants were simultaneously shown one or three fractals in pseudo-random locations. After a delay of either 1 or 4 seconds, they made a two-alternative forced choice between one

of the previously encoded fractals and a foil. Participants were instructed to select the previously seen fractal and drag it to its remembered location. Their findings indicated that participants with LE displayed larger errors when several items had to be remembered, but not for a single item (Pertzov et al., 2013).

Additionally, LTM impairment in individuals with LE has been evident in several studies using a broad range of tests. Using a comprehensive neuropsychological test battery to assess cognitive function longitudinally in participants with LE, Butler et al. (2014) showed that they may experience permanent LTM deficits despite making a substantial recovery in other cognitive domains (Butler et al., 2014). More recently, Argyropoulos et al. (2019) characterised the same LE cohort and specified that they showed pronounced episodic memory retrieval impairment of both verbal and visual material, demonstrating prominent forgetting of visual material (Argyropoulos et al., 2019).

Despite all the evidence pointing towards both WM and LTM degradation in individuals with MTL damage, the two memory systems have been studied independently, using different measures and methods that do not allow for their direct comparison. Instead, using tasks with identical stimuli and response requirement to compare performance between the two types of memory could shed light on novel aspects of their mechanisms both in LE and in healthy individuals.

Previous chapters discussed the crucial role the MTL, and particularly the hippocampus, plays in spatial memory and navigation. For this reason, using a task to measure these abilities in both WM and LTM may provide a more sensitive measure of the two memory systems, and indirectly of the integrity of MTL systems, based on allocentric spatial associations.

This chapter builds on knowledge acquired in previous chapters focused on healthy individuals, and on earlier research emphasising the value of clinical cohorts. I used a spatial memory task based on navigation to measure and compare WM and LTM in two groups of elderly individuals, one healthy and one with LE. The tasks used identical stimuli and response

requirements. I expected to find a decrease in both spatial WM and LTM in the LE group, compared to healthy individuals. Additionally, I predicted a steeper decrease in memory quality from WM to MTM for participants with LE.

4.2 Methods

4.2.1 Participants

This study was approved by the South-Central Oxford Research Ethics Committee (research ethics project number: 08/H0606/133) and was conducted according to the Declaration of Helsinki. All participants provided their informed consent prior to taking part in the study and were reimbursed for their time at a rate of £10/hour, as well as for their travel to the testing venue.

Thirty older participants (14 females, 16 males, ages range 62-81, M = 71.9, SD = 5.8) were recruited from the Friends of Oxford Dementia and Ageing Research platform (https://www.oxdare.ox.ac.uk/home). Two participants were excluded from the analysis, as they experienced nausea performing the task and the experiment had to be ceased. An additional seven participants were excluded from the analysis because they were unable to perform the task above chance level (see Analysis section). The remaining twenty-one participants were included in the final set of analyses (10 female, 11 male, age range 63-79, M = 71.26, SD = 2.5).

Additionally, data were collected from nine participants with autoimmune LE (1 female, 8 males, ages range 61-82, M = 67.88, SD = 7.4) identified by Dr Chris Butler at the Russell Cairns Unit of the John Radcliffe Hospital in Oxford (Table 4.1). All patients had undergone neuropsychological assessment during the acute phase of the illness and had been diagnosed with LE according to the diagnostic criteria described earlier (Graus et al., 2016). Tumours, herpes simplex virus encephalitis, and other infectious aetiologies were excluded as potential diagnoses using suitable serum and CSF tests. All participants in the LE group had

been previously treated with immunotherapy (e.g., intravenous and/or oral steroid medication, plasma exchange) in the acute phase of the illness and were taking epilepsy medication at the time of data collection, as the seizures characteristic to the acute phase of the disease could still be present in the post-acute phase (Table 4.1). Anticonvulsants supress seizures either by changing neurons' electrical activity, affecting ion channels in the cell membrane, or by modifying chemical transmission between neurons, or affecting neurotransmitters in the synapses. Side effects to these medications are common particularly early in their administration. These include nausea, abdominal pain, dizziness, sleepiness, irritability, anxiety, or mood changes. However, these have not been shown to affect individuals' memory or navigation abilities (Doty, Rudd, Stoehr, & Thomas, 2007; Goldberg & Burdick, 2001; Goldsmith, Wagstaff, Ibbotson, & Perry, 2003; Li, Sun, & Wang, 2020; Lyseng-Williamson, 2011).

LE participants had brain MRI scans both during the acute phase of the disease, and in the post-acute phase. The volumetric analyses of their post-acute MRIs revealed pronounced MTL atrophy, specifically in both the left and the right hippocampus, and reduced thalamic volumes. The larger LE cohort from which the current participants were selected also presented with reduced volumes of the entorhinal cortex. However, that was not the case for the nine participants included. A more detailed description of the imaging data of the LE cohort that the nine patients were part of was published by Argyropoulos and colleagues (2019) (Argyropoulos et al., 2019). Additionally, the manually delineated hippocampal volumes regressed against participants' age, sex, total intracranial volume and scanning protocol and z-scored against a cohort of healthy age-matched individuals are also included in Table 4.1. A z-score of 0 represents the mean hippocampal volume of the healthy cohort. The composite z-scores of recall derived from age-scaled scores for each participant relative to population-based norms for WMS-III (Word Learning (Immediate Recall), Word Learning (Delayed Recall), Logical Memory (Immediate Recall), Logical Memory (Delayed Recall)), People subtest from the Doors and People test, Shapes subtest from the Doors and People test,

Rey-Osterrieth Complex Figure Test Immediate and Delayed recall and subsequently averaged, are also included in Table 4.1.

It is important to note that the dataset presented in this study is incomplete. Twelve additional participants with LE had been recruited and were scheduled for testing in March and April 2020. However, due to the ongoing COVID-19 pandemic all data collection was halted and could not be resumed on time for the completion of this thesis, as the target participants belong to a high-risk group. In the interest of completeness, both descriptive and statistical results are presented below. Since the study was based on a small sample size, it was statistically underpowered. Accordingly, any statistical outcomes should only be interpreted in relation to this particular cohort and should not be the basis for any further generalisation.

Table 4.1

Demographics of participants with LE. The table provides information about participants' age at time of testing (years), age at symptom onset (years), sex, years of education (years), medication at time of testing, the z-scores of manually delineated hippocampal volumes (regressed against participants' age, sex, total intracranial volume and scanning protocol) and average composite z-scores of recall derived from age-scaled scores for each participant relative to population-based norms for WMS-III (Word Learning (Immediate Recall), Word Learning (Delayed Recall), Logical Memory (Immediate Recall), Logical Memory (Delayed Recall)), People subtest from the Doors and People test, Shapes subtest from the Doors and People test, Rey-Osterrieth Complex Figure Test Immediate and Delayed recall

Participant with LE	Age	Age at symptom onset	Sex	Years of education	Antibodies	Medication at time of testing	Hippocampal volume	Recall score
1	79	65	M	11	LGI1	Dutasteride, Evacal, Lansoprazole, Levetiracetam, Phenytoin sodium	-.61	.10
2	61	51	M	10	Caspr2	Perindopril, Simvastatin, Lamotrigine, Zonisamide, Brivaracetam	-.22	-.10
3	67	60	M	12	Caspr2	Lamotrigine	-1.44	-1.77
4	68	63	M	12	LGI1	Lacosamide	-.44	.35
5	70	52	M	13	LGI1	Lansoprazole, Calceos	-1.29	.30
6	82	69	F	12	Caspr2	Lamotrigine, Calceos, Amlodipine, Pravastatin	-.55	.00
7	61	56	M	11	LGI1	Lacosamide	-.39	.25
8	62	44	M	12	LGI1	Levetiracetam, Phenytoin sodium	-1.95	-.16
9	61	35	M	14	LGI1	Lamotrigine	-2.22	-2.09

All participants with LE were able to tolerate the task and complete the experiment. All of them were also fluent in English and had normal or corrected-to-normal vision and hearing. The two groups were matched both for age ($t(28) = 0.04$, $p = 0.96$) and years of education ($t(28) = 1.8$, $p = 0.82$) (Table 4.2).

Table 4.2

Means and standard deviations of all participants' ages and years of education, divided by group. The groups did not differ significantly in their mean scores in either of the two measures.

Measure	Healthy participants	Participants with LE	Significance
Age, mean (SD)	71.3 (2.5)	74.4 (10.6)	0.96
Years of education, mean (SD)	12.1 (3.8)	11.8 (2.3)	0.82

4.2.2 Experimental setup

Healthy participants completed the experiment in a group testing room in the Department of Experimental Psychology of the University of Oxford with a capacity of 20 people, although no more than 3 people were tested at one time. Participants each sat approximately 50 cm from the monitor (Dell U2312HM Monitor, 1920 x 1080 resolution; refresh rate 60 Hz). Data from participants diagnosed with LE were collected during home visits by the researcher. Participants completed the task on a laptop (Lenovo ThinkPad X1 Carbon, 1920 x 1080 resolution, refresh rate 60 Hz), while they were seated at a table, approximately 50 cm away from the screen.

To navigate through the task environments, participants were instructed to use the mouse and WASD keys of the keyboard. The mouse was used to change the direction of the gaze, whereas the keyboard was used to move forward (W), backward (S), to the right (D) and to the left (A). If participants were not able to navigate using the mouse and keyboard, the researcher offered to operate the hardware following the participants verbal instructions. This was necessary for four of the twenty-one healthy participants, and one of the participants with LE. In this case, the researcher instructed the participants to trace the desired path with their finger on the monitor during navigation, while offering verbal cues to describe the desired trajectory at all times (e.g., "go forward", "stop", "turn left/right", "turn around").

4.2.3 Protocol

Healthy participants performed the study in two sessions, over successive days. They completed two different studies during these sessions: the navigation memory study,

discussed in the current chapter, and the study investigating attention in memory (discussed in Chapter 2). Additionally, only the first session of this study is included in the current chapter. Participants' performance on the second day is reviewed in Chapter 3. Participants received instructions about both studies; they were given a chance to familiarise themselves with the apparatus and to train on the tasks and they completed the first experimental testing session for each study. In addition, participants completed an online set of questionnaires including the Pittsburgh Sleep Quality Index.

Participants diagnosed with LE were tested separately. They also performed two additional tasks within the same session: one measuring their emotional lability, which will not be discussed in this thesis, and another one measuring individuals' approach avoidance behaviour conducted by another researcher. Similarly, they also received instructions about all studies, were given a chance to get accustomed to the hardware and to train on the tasks, and they completed the experiments for each study. Participants with LE also completed an online set of questionnaires pertaining to their emotionality.

For the current study, for both cohorts, testing started with an introduction from the researcher about the general purpose of the study and the hardware participants were asked to use throughout the task. Next, participants proceeded to perform a practice session, to ensure they were comfortable using the mouse and keyboard to navigate. If they were not able to navigate using the mouse and keyboard after 10 minutes of practice, the researcher offered to operate the hardware following the participants verbal instructions. Following the practice session, participants completed the first experimental session of this study. This consisted of two testing blocks, separated by a 20-minute break. During the break, participants completed their respective online questionnaires.

4.2.4 Behavioural Stimuli

The behavioural stimuli used in this study are described in Chapter 3. For a detailed presentation, refer to section 3.3.1.4. The adjustments involved eliminating the second session, typically performed on the second consecutive day.

4.2.5 Behavioural Task

The task used in this study is identical to the one used during the first session of the experiment presented in Chapter 3. To recap, the task was used to measure and compare spatial memory retrieval at different timepoints in the two cohorts. Participants had to search for and keep in mind the location of everyday objects within five virtual environments. First, they explored and looked for two objects in a simplified environment with no obstacles. This helped participants adjust to the technology and commands. Subsequently, testing was arranged into search and retrieval blocks. Retrieval was measured at two timepoints and divided into Working Memory (WM), measured after every search block, and Medium-term Memory (MTM), measured after a 20-minute break. Considering that the same task was used as the one previously described in the second study of Chapter 3, these labels assigned to the two measures are maintained and used for continuity and clarity purposes, following Chapter 3. Conceptually, MTM blocks measured participants' long-term memory performance.

As previously described, the task began with three blocks of interleaved search and WM trials. Each block consisted of five search trials, each followed by a WM trial, one for every environment. After the three blocks, participants answered a series of questionnaires during a 20-minute break from the task. Next, they completed one MTM block of five trials, one for each environment (Figure 3.11). Participants were not informed about the experimental timeline in advance. Each type of block is thoroughly described in section 3.3.1.4.

4.2.6 Analysis

The main aim of the analyses was to compare the MW and LTM spatial memory performance of the healthy control vs LE groups to determine whether and how retrieval performance differs for participants with MTL damage. The dependent measures computed were search accuracy, distance error, response time and proportion of swaps. During search trials, an object was considered found if the participants responded within 2 vm from the object. Similarly, retrieval trials were considered correct if participants' responses were within 2 vm from the correct target object location.

Search accuracy was calculated as the percentage of total objects found by each participant in each trial of the search phase of the experiment. Distance error was computed as the Euclidian distance between the response position and the correct position of the respective object in virtual meters. This measure was used to analyse participants' performance in all stages of the experiment. Response time was measured from the start of each trial, when the participant was placed in the environment, until an object was found, or until the participant made a response for a remembered location and was normalised by the distance between the start and the target location.

Lastly, using a similar method as Pertzov et al. (2013), the proportion of swaps was calculated as the percentage of retrieval trials in which participants responded within 2 vm from the location of the non-selected object associated with the same environment for the respective trial (Pertzov et al., 2013).

Data were processed and statistically analysed using the R software. Mixed-model ANOVAs were used to test the effect of group and block number on search and WM performance. Out of the three WM trials, only the first measured pure working memory performance (since memory measures in subsequent trials may have combined working memory in current trial and prior memory from previous trials). Therefore, paired-sample t-tests were used to compare participants' working memory distance errors and response times. Additional mixed-model ANOVAs were used to test the effect of group and memory timepoint

on performance and to compare their performance in WM and MTM. Lastly, distance errors and response times in the first WM block and during MTM retrieval were also correlated with two other measures available for the LE group, previously collected for a different study (Argyropoulos et al., 2019): the manually delineated hippocampal volumes regressed against participants' age, sex, total intracranial volume and scanning protocol, and the composite z-scores of recall derived from age-scaled scores for each participant relative to population-based norms for WMS-III (Word Learning (Immediate Recall), Word Learning (Delayed Recall), Logical Memory (Immediate Recall), Logical Memory (Delayed Recall)), People subtest from the Doors and People test, Shapes subtest from the Doors and People test, Rey-Osterrieth Complex Figure Test Immediate and Delayed recall and subsequently averaged. Prior to conducting these statistical tests, the assumption of homogeneity of variance was tested using Levene's test, whereas the normality of the distribution of the values was visualised using histograms, the values of skewness and kurtosis, and tested using the Shapiro-Wilk test. All assumptions were met.

4.3 Results

4.3.1 Search Results

Both groups showed similar levels improvement during the navigation search trials, reaching approximately 90% accuracy after the three blocks. The changes in response times were also similar, both groups becoming faster after every block (Figure 4.2).

First, search accuracy was calculated as the percentage of trials in which participants successfully found the target object. For a trial to be considered correct, participants had to be within 3 vm from the target location. A mixed-model ANOVA with group as the between-subject factor and block number as the within-subject factor showed a significant main effect of block ($F(2,28) = 9.03$, $p < .001$, $\eta^2 = .2$), reflecting improvement in performance across time for both groups. The main effect of group was not significant ($F(1,28) = 0.01$, $p = .5$, $\eta^2 = .009$), suggesting that both cohorts performed at similar levels during search blocks. Moreover,

group and block number did not interact significantly ($F(2,28) = 0.4$, $p = .27$, $\eta^2 = .01$), implying that the two groups had similar patterns of learning across the three search blocks (Figure 4.2 A).

Another measure of learning during search was response time, calculated for each block and collapsed across trials. An ANOVA with group as the between-subject factor and block as the within-subject factor revealed a main effect of block number ($F(2,28) = 11.73$, $p < .001$, $\eta^2 = .23$). There was no significant effect of group ($F(1,28) = 4.27$, $p = .36$, $\eta^2 = .02$), or group x block interaction ($F(2,28) = 2.89$, $p = .07$, $\eta^2 = .03$) (Figure 3.14 B). These results indicate that both groups responded faster over time (Figure 4.2 B).

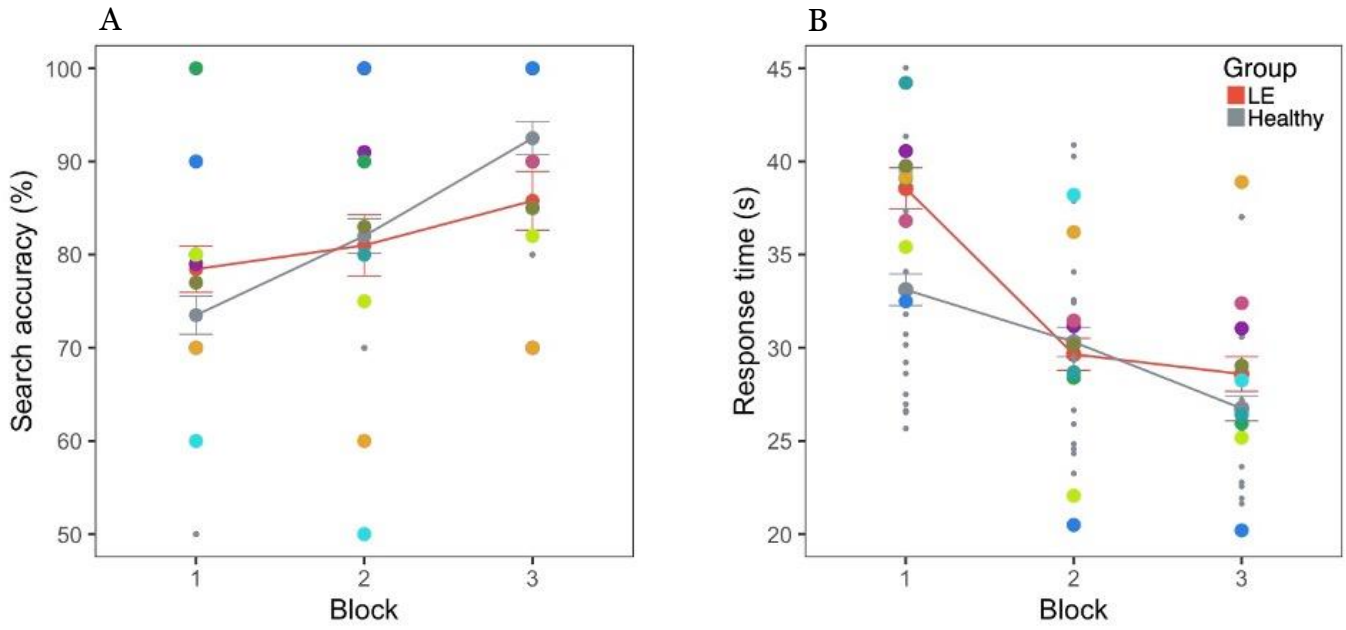

Figure 4.2 A. Average search accuracy across all objects and environments for healthy participants and individuals with LE. Participants improved across the three blocks B. Average response time across all objects and environments for healthy participants and individuals with LE, indicating that both groups improved over time. The error bars represent the standard error of the mean. Each point represents an individual participant's response. The coloured points represent individuals with LE, whereas the smaller grey points represent healthy individuals. Each individual with LE is represented with a different colour in an effort to identify patterns of performance within the LE group.

4.3.2 Retrieval Results

4.3.2.1 Working Memory

The WM trials refer to the retrieval trials that followed each search. To assess participant's ability to retrieve the learned locations, distance errors and response times were calculated for each age group, averaging across all objects and environments. To compare the true working memory retrieval abilities of the two groups, first, their distance errors from the first WM block were investigated. The two groups demonstrated similar distance errors, while participants with LE were slower to respond compared to healthy participants.

An independent samples t-test revealed that the difference between the two groups' errors was not significant ($t(28) = -0.502$, $p = .1$, $d = .4$), suggesting that healthy participants and participants with LE were similarly precise (Figure 4.3 A). Additionally, neither the correlation between LE participants' distance errors and their hippocampal volumes ($r(7) = -.15$, $p = .79$) nor the one between their errors and their composite recall scores ($r(7) = -.06$, $p = .65$) was significant.

Similarly, participants' response times were compared for the first WM block using an independent sample t-test. This revealed that healthy participants were significantly faster to respond compared to participants with ($t(28) = 3.16$, $p = .002$, $d = .6$) (Figure 4.3 B). Neither the correlation between LE participants' response times and their hippocampal volumes ($r(7) = -.21$, $p = .09$) nor the one between their errors and their composite recall scores ($r(7) = -.16$, $p = .75$) was significant.

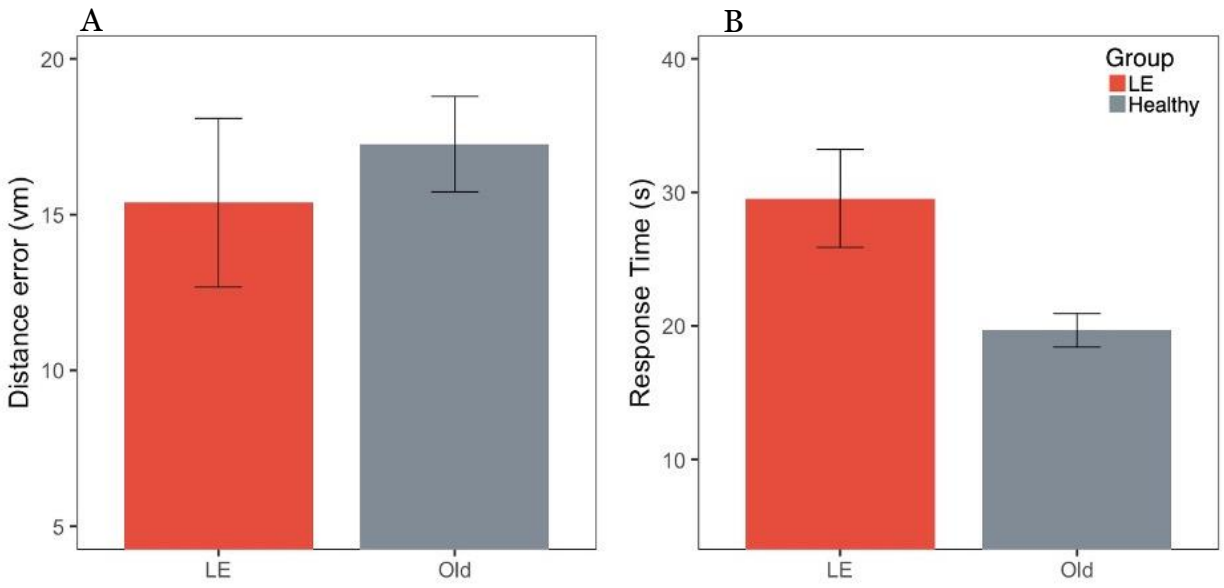

Figure 4.3 A. Average distance error across all objects and environments for healthy participants and individuals with LE in the first WM block. Healthy participants and participants with LE were similarly precise. The error bars represent the standard error of the mean B. Average response time across all objects and environments for healthy participants and individuals with LE in the first WM block, indicating that healthy participants responded faster compared to individuals with LE. The error bars represent the standard error of the mean.

When looking at all retrieval trials following search in subsequent learning blocks, the results suggested that both groups improved across the three blocks in terms of their distance errors, and that healthy participants were overall faster than participants with LE.

An ANOVA with group as the between-subject factor and block as the within-subject factor was performed to analyse distance errors. This revealed a main effect of block number ($F(2,28) = 4.81$, $p = .03$, $\eta^2 = .12$), suggesting that both groups' performance changes significantly over time. However, the main effect of group ($F(1,28) = 0.01$, $p = .89$, $\eta^2 = .001$) and the group x block interaction ($F(2,28) = 1.31$, $p = .27$, $\eta^2 = .04$) were not significant (Figure 4.4 A).

Next, a mixed-model ANOVA comparing mean response times with group as the between-subject factor and working-memory block number as the within-subject factor revealed a significant main effect of group ($F(1,28) = 16.02$, $p < .001$, $\eta^2 = .19$), reflecting faster

responses for healthy participants compared to participants with LE. The main effect of block number was not significant ($F(2,28) = 0.82$, $p = .05$, $\eta^2 = .02$), indicating that participants maintained a relatively constant response time across the three blocks. There was no interaction between group and block ($F(2,28) = 1.27$, $p = .28$, $\eta^2 = .04$ (Figure 4.4 B).

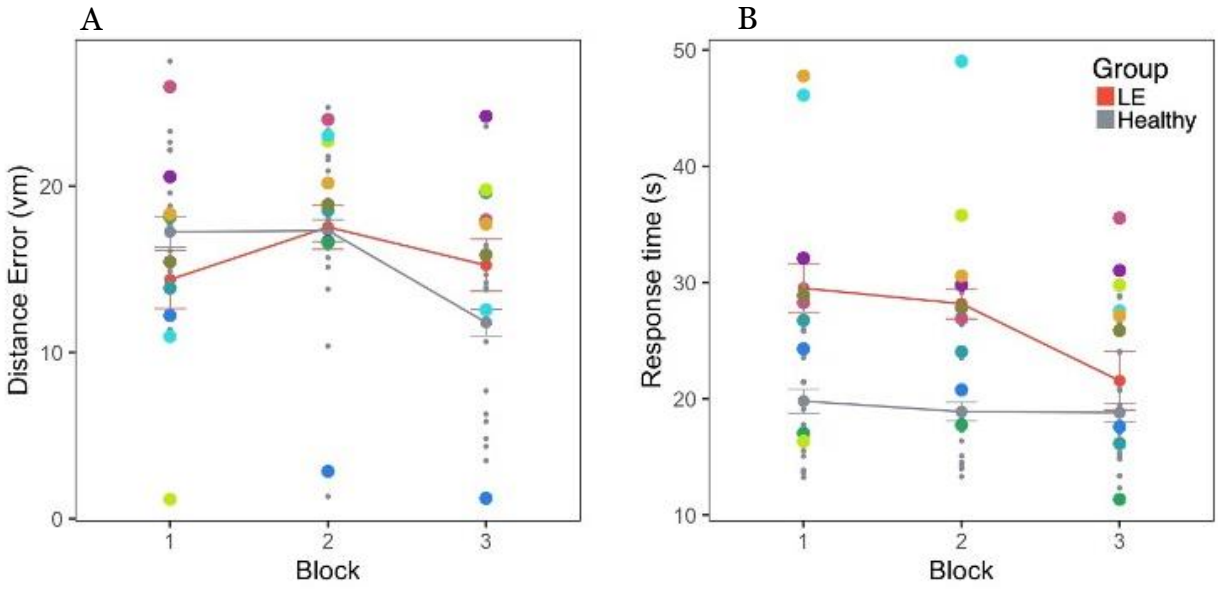

Figure 4.4 A. The plot shows the average distance error during each WM block for healthy participants and individuals with LE. The error bars represent the standard error of the mean. The figure shows an improvement in performance throughout the three blocks for the two groups. B. The plot shows the average response time across all objects and environments trials for healthy participants and individuals with LE. The error bars represent the standard error of the mean. This illustrates the fact that healthy participants were faster overall compared to individuals with LE. The coloured points represent individuals with LE, whereas the smaller grey points represent healthy individuals. Each individual with LE is represented with a different colour in an effort to identify patterns of performance within the LE group. Individuals are assigned the same colour in all figures.

4.3.2.2 Long-Term Memory

Participants' long-term memory was measured during retrieval trials carried out 20 minutes after completing the search blocks (MTM condition in Chapter 3) and compared to retrieval immediately after the last WM block after all search blocks and learning was completed. To assess their ability to retrieve the learned locations, distance errors, response times and proportion of swaps were calculated for each group, averaging across all objects and environments. The differences identified stemmed from their response times, with LE participants responding slower compared to healthy individuals.

First, an ANOVA with group as the between-subject factor and timepoint as the within-subject factor was performed to compare the two groups' distance errors. This revealed that neither the main effect of group ($F(1,28) = 4.1$, $p = .07$, $\eta^2 = .1$) nor the main effect of timepoint ($F(1,28) = 1.31$, $p = .4$, $\eta^2 = .01$) was significant. The interaction between age and timepoint was also not significant ($F(1,43) = 0.49$, $p = .49$, $\eta^2 = .005$) (Figure 4.5 A). The results remained consistent when adjusting for the number of times each target object was found during search trials. When correlating participants' errors and their hippocampal volumes the results were not significant ($r(7) = -.29$, $p = .59$). Similarly, the correlation between their errors and their composite recall scores ($r(7) = -.13$, $p = .62$) was also not significant.

Next, the source of distance errors was investigated. Swap percentages were compared using an ANOVA with group as the between-subject factor and timepoint as the within-subject factor. This did not reveal any significant result. The main effect of group ($F(1,28) = 0.23$, $p = .61$, $\eta^2 = .01$) suggested that healthy and LE participants swapped the locations of the two objects associated with the same environment with similar frequencies, whereas the non-significant effect of timepoint ($F(1,28) = 0.03$, $p = .86$, $\eta^2 = .01$) indicated that both groups remained consistent after the 20 minute break. The interaction between group and timepoint was also not significant ($F(1,28) = 0.3$, $p = .89$, $\eta^2 = .01$) (Figure 4.5 B). The results remained consistent when adjusting for the number of times each target object was found during search trials.

Lastly, response times were compared between the two groups for the three time points using an ANOVA with age as the between-subject factor and timepoint as the within-subject factor. This revealed a significant main effect of group ($F(1,28) = 13.04$, $p = .004$, $\eta^2 = .33$), with healthy participants responding significantly faster compared to participants with LE. Neither the main effect of timepoint ($F(1,29) = 3.56$, $p = .07$, $\eta^2 = .02$) nor the interaction between group and timepoint ($F(1,28) = 2.22$, $p = .15$, $\eta^2 = .01$) was significant (Figure 4.5 C). The results remained consistent when adjusting for the number of times each target object was found during search trials. Finally, when correlating participants' MTM errors and their

hippocampal volumes the results were not significant ($r(7) = -.17$, $p = .74$). Similarly, the correlation between their errors and their composite recall scores ($r(7) = -.19$, $p = .43$) was also not significant.

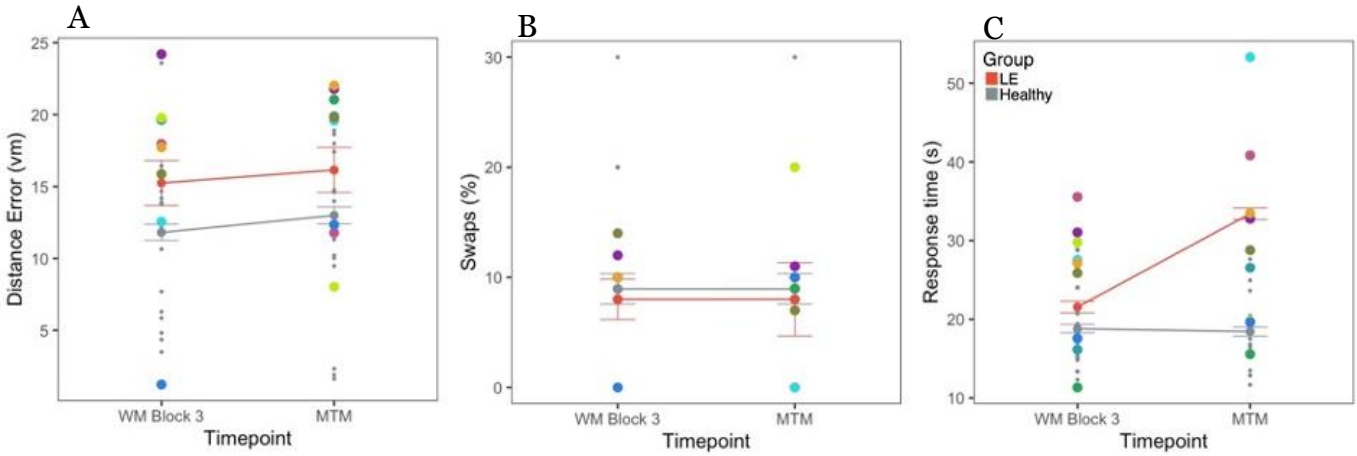

Figure 4.5 A. The plot shows the average distance error during the last WM block and during the MTM retrieval trials for healthy participants and individuals with LE. The error bars represent the standard error of the mean. Each point represents an individual participant's response. B. The plot shows the average swap percentage across all objects and environments for healthy participants and individuals with LE during the last WM block and during MTM retrieval. The error bars represent the standard error of the mean. C. The plot shows the average response time across all objects and environments for healthy participants and individuals with LE. The error bars represent the standard error of the mean. This illustrates the fact that healthy participants were faster overall compared to individuals with LE. Each point represents an individual participant's response. The coloured points represent individuals with LE, whereas the smaller grey points represent healthy individuals. Each individual with LE is represented with a different colour in an effort to identify patterns of performance within the LE group. Individuals are assigned the same colour in all figures.

4.3.2.3 Working and Medium-Term Memory

Next, to investigate participants' performance and the relationship between different memory systems, the first WM block and the MTM retrieval trials were compared. The results revealed that whereas healthy participants' distance errors decreased from WM to MTM, participants with LE did not show any improvement. Additionally, individuals with LE were slower to respond compared with healthy participants.

First, distance errors were calculated and averaged across objects and environments for all participants and timepoints. An ANOVA with group as the between-subject factor and

retrieval timepoint as the within-subject factor was performed. The results revealed a that the main effect of timepoint ($F(1,28) = 0.2$, $p = .6$, $\eta^2 = .01$), as well as the main effect of group ($F(1,28) = 0.8$, $p = .3$, $\eta^2 = .01$) were not significant. The interaction between group and timepoint was borderline significant ($F(1,28) = 3.9$, $p = .05$, $\eta^2 = .05$). However, this indicated that whereas healthy participants seemed to at least qualitatively improve in their performance, participants with LE did not (Figure 4.6 A).

Next, the source of distance errors was investigated. Swap percentages were compared using an ANOVA with group as the between-subject factor and timepoint as the within-subject factor. This did not reveal any significant result. The absence of a main effect of group ($F(1,28) = 0.05$, $p = .81$, $\eta^2 = .01$) suggested that healthy and LE participants swapped the locations of the two objects associated with the same environment at similar rates, and the non-significant effect of timepoint ($F(1,28) = 0.12$, $p = .73$, $\eta^2 = .03$) indicated that both groups remained consistent after the 20 minute break. The interaction between group and timepoint was also not significant ($F(1,28) = 0.12$, $p = .72$, $\eta^2 = .03$) (Figure 4.6 B).

The last variable measured to compare retrieval performance was response time. Another mixed-effects ANOVA was performed, with response time as the dependent variable, group as the between-subject factor and timepoint as the within-subject factor. The results revealed a significant main effects of group ($F(1,28) = 22.63$, $p < .001$, $\eta^2 = .33$), showing healthy participants to be faster than participants with LE. Both the main effect of timepoint ($F(1,28) = 0.002$, $p = .03$, $\eta^2 = .02$) and the interaction between group and timepoint were not significant ($F(1,28) = 1.06$, $p = .3$, $\eta^2 = .02$) (Figure 4.6 C).

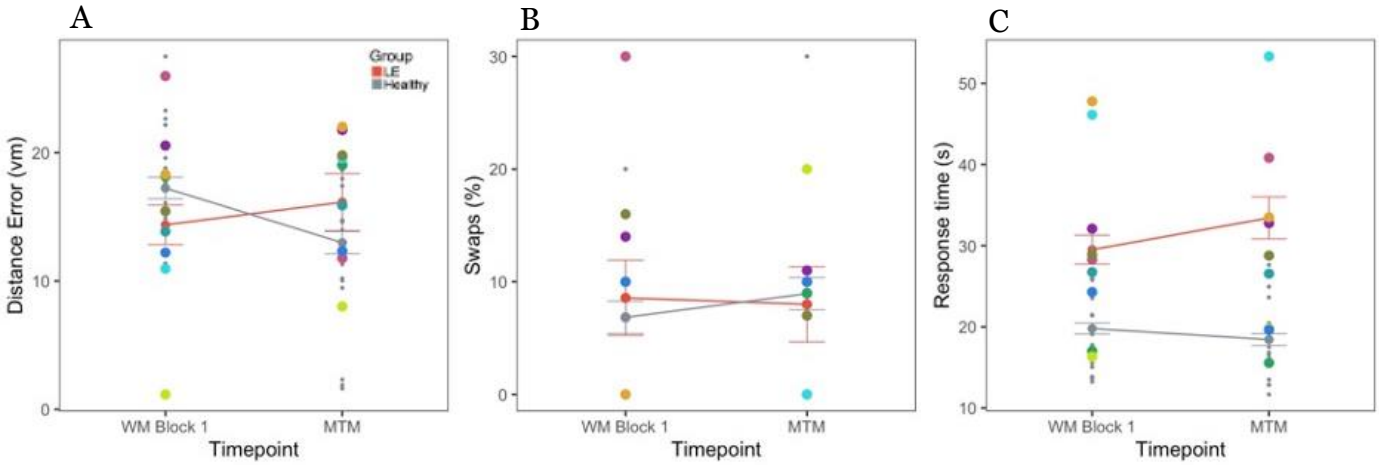

Figure 4.6 A. The plot shows the average distance error during the first WM block and during the MTM retrieval trials for healthy participants and individuals with LE. The error bars represent the standard error of the mean. Each point represents an individual participant's response. B. The plot shows the average swap percentage across all objects and environments during the first WM block and during the MTM retrieval trials for healthy participants and individuals with LE. The error bars represent the standard error of the mean. C. The plot shows the average response time across all objects and environments trials during the first WM block and during the MTM retrieval trials for healthy participants and individuals with LE. The error bars represent the standard error of the mean. This illustrates the fact that healthy participants were faster overall compared to individuals with LE. Each point represents an individual participant's response. The coloured points represent individuals with LE, whereas the smaller grey points represent healthy individuals. Each individual with LE is represented with a different colour in an effort to identify patterns of performance within the LE group. Individuals are assigned the same colour in all figures.

4.4 Discussion

The current study used a novel continuous report spatial navigation task to investigate the effects of MTL damage on working and long-term memory performance, compared to healthy ageing. It was expected that individuals with LE would show a decrease in spatial abilities for both WM and LTM, compared to the healthy group throughout the task. Additionally, I predicted a decrease in memory quality with time for healthy adults, and a worse performance with time for participants with LE. In the circumstances of the ongoing COVID-19 pandemic, my initial predictions could not be tested fully, and the results remain inconclusive because of the small number of participants and low statistical power. However, for completeness, they are discussed below, accompanied by suggestions for future studies.

First, contrary to expectations, participants diagnosed with LE were not impaired in their search performance, compared to healthy individuals, as indicated by the accuracy of finding the target objects in the virtual environments. Previously, Chun and Phelps (1999) used a contextual cuing task that relies on intact memory for contextual information that can be considered implicit and found that amnesic individuals with MTL impairment had reduced implicit contextual learning (Chun & Phelps, 1999). Additionally, in the current study, search blocks relied mostly on participants' ability to use mouse and keyboard to navigate freely in the virtual environments. In this case, the better they were able to navigate around the environment, the bigger the areas they could cover, which increased their chances of finding the target objects, even by chance. What is more, the fact that both groups showed an increase in search accuracies and a decrease in response times could indicate the fact that they became more accustomed to navigating in the virtual environments with every block, and not necessarily that they were learning.

When comparing participants' pure working memory performance, individuals with LE were slower, despite remembering the object locations similarly to healthy individuals. This does not reflect any difference in memory quality and opposes previous findings investigating working memory retrieval in an LE cohort that the current individuals were part of. These results mirror participants' performance during search trials. Additionally, compared to the Pertzov et al. (2013) study, in this case participants were not asked to also remember the objects' identities, which could have increased the cognitive load and difficulty of the task (Pertzov et al., 2013).

Comparing participants' performance on the three WM blocks, despite both groups' performance changing significantly in terms of their distance errors, healthy adults qualitatively improved their performance, whereas LE individuals did not. Similarly, when comparing participants' performance on the first WM block and the MTM block, healthy participants showed a qualitative improvement in their distance errors, whereas participants with LE did not, Additionally, healthy adults were faster compared to participants with LE.

These findings are congruent with previous research conducted by Guderian et al. (2015) who used an adapted virtual maze task to measure spatial and navigational abilities of individuals with moderate and severe hippocampal damage. Similarly, after the first search block, they instructed participants to place the objects back in the environment, one by one. After each response the targets would appear in their original location, and participants were asked to collect them just like in the search block. When testing whether learning rates differed among the three groups, results showed that whereas healthy participants and those with mild hippocampal damage improved significantly across all blocks, participants with severe impairment did not (Guderian et al., 2015).

Additionally, the overall errors did not differ between the two groups. Another series of studies showed that for individuals with MTL damage impairment is evident when several items need to be retrieved after a short delay, but not for single items (Jeneson, Mauldin, & Squire, 2010; Jeneson, Wixted, Hopkins, & Squire, 2012). What is more, Pertzov el at (2013) found that WM impairment was observed when three objects and their locations had to be retrieved, but not for only one item. This study also concluded that the impairment observed when maintaining multiple items in WM does not reflect poor memory of individual object features, but instead it is caused by an inability to bind different features together, which likely involves the MTL (Pertzov et al., 2013). This might be the case for the current study as well. However, measuring participants' retrieval of a set size of 2 objects, retrieved one by one might not have been sufficiently sensitive to identify actual deficiencies caused by LE. To address this, future studies could alternate the number of objects in each environment, allowing for a comparison between different set sizes as well.

What is more, when comparing the two cohorts' performance in WM and LTM, the results contradicted the original hypotheses. These showed that overall, the two groups did not differ in their errors when retrieving target locations. These results also contradict previous consensus that participants with LE show deficits in episodic memory (Christopher R. Butler et al., 2014; Finke et al., 2017; Irani et al., 2013). What is more, earlier studies have

also established that reduced hippocampal volumes predict reduced allocentric spatial memory and navigational abilities in similar virtual environments (Guderian et al., 2015).

A possible explanation for the lack of a significant interaction between group and memory type, in this case, could be the small sample size which only allowed for underpowered statistical tests. Alternatively, using a virtual reality spatial memory task and fMRI in healthy individuals, Doeller et al. (2008) showed that while the hippocampus was critical for retrieving locations relative to environmental boundaries, remembering locations relative to environmental landmarks was connected to the activation of the caudate nucleus (Doeller & Burgess, 2008). This outcome is also consistent with findings in rodent experiments (Packard & McGaugh, 1996; Pearce, Roberts, & Good, 1998). Extrapolating to the current study, where the boundaries were not clearly marked in all environments, which instead provided numerous landmarks, the absence of decreased performance in individuals with LE could suggest that they might have been able to retrieve objects' locations relative to local landmarks, due to their previously demonstrated spared caudate (Argyropoulos et al., 2019). For this reason, follow-up studies could consider a distinction in their environments' design that could separate boundary-based from landmark-based navigation.

The most impactful limitation of this study was the sample size of the LE group which, like in most studies involving a similar clinical cohort, was very small. This study was thus susceptible to confounds such as impairment heterogeneity, measurement noise and individual differences (Lambon Ralph et al., 2002). Guderian et al. (2015) studied allocentric spatial memory retrieval in healthy participants, individuals with moderate hippocampal damage, and individuals with severe hippocampal damage. They found that, despite participants with severe damage showing memory impairment, those with moderate damage did not differ from healthy individuals in their performance (Guderian et al., 2015). In the current study, it is possible that the heterogeneity in hippocampal damage to be reflected similarly in a lack of difference between the two groups, exacerbated by small statistical power. In an effort to identify representative individual cases, participants with LE were examined

separately as well as at a group level, and patterns were searched for guided by their hippocampal volumes and composite recall scores previously calculated by Argyropoulos et al. (2019) (Argyropoulos et al., 2019). This attempt was unsuccessful. However, despite the small number of participants and low statistical power, I was able to appreciate how other modifications to the task might add power, sensitivity, informativeness for future studies.

When designing a task aimed to assess WM and LTM performance of similar cohorts, future studies should also consider increasing the number of trials for each type of block. One limitation of this study is the low number of trials available for analysis of each condition. Increasing the number of retrieval trials, would allow for additional statistical analyses that could help identify more reliable possible reasons for observed behaviour. For example, mixture modelling could shed some light on the potential sources of distance errors, identifying guesses and swap rates in more accurate ways.

To analyse navigational abilities at different timepoints separately from participants' spatial memory of objects' locations, an additional phase could be added to the task. This would involve asking participants to retrieve previously encoded objects' locations statically. An allocentric perspective could be ensured by placing them in a new position at the start of each trial for a change in perspective and asking them to click on the remembered location. What is more, to also distinguish impaired object-location association mechanisms from decreased navigation abilities, each phase of the task should include an increased number of trials to allow for identification of the sources of error.

Lastly, it is not only the decreased hippocampal volumes that could modulate the results, but also the locus of the impairment. In an fMRI experiment, Nadel et al. presented participants with arrays of objects and asked them to form associations between pairs based either on the spatial relations between the objects or a comparison of other nonspatial features. They found that spatial relational judgments resulted predominantly activated the posterior hippocampus, while nonspatial judgments were limited to the anterior hippocampus (Nadel, Hoscheidt, & Ryan, 2013). Additionally, Evensmoen et al. (2013) also observed a shift

in activation from processing global spatial representations in the anterior hippocampus to processing more detailed, local spatial information which mainly relies on the posterior hippocampus (Evensmoen et al., 2013). Lastly, another view was proposed that suggests that the posterior hippocampus is predominantly involved in memory and spatial navigation, whereas the anterior hippocampus modulates emotional behaviours, due to its increased connectivity with the amygdala and hypothalamic endocrine and autonomic nuclei (Strange, Witter, Lein, & Moser, 2014). Therefore, different navigational strategies could be differently impacted by hippocampal impairment depending on the location of the damage. For this reason, future studies should also consider the location of the impairment along the anterior-posterior hippocampal axis.

To my knowledge, this is the first study to compare the spatial memory and navigational skills of healthy older adults and individuals with MTL impairment using identical stimuli and response requirements at different timepoints. Despite the underpowered statistics caused by an incomplete dataset, it was encouraging that LE participants were able to tolerate the task well. The findings presented should not be generalised to a larger LE population. However, the methods and analyses presented should certainly be explored further, using an adapted version of this task and a larger sample size, as this could provide invaluable information about the different patterns of use of the two memory systems in ageing and disease.

5. General Discussion

The associative feature of our memory allows us to make sense of the world around us by connecting the plethora of stimuli invading our senses to build experiences and episodes. It also represents a shared feature of WM and LTM and hence an avenue to explore their shared mechanisms, differences, and relationship. Additionally, space represents an essential dimension along which we form memories of the contexts associated with these experiences and remembering objects' locations becomes an essential aspect of our everyday lives.

The overarching aim of this thesis was to explore MTL-mediated WM and LTM retrieval in ageing and disease and their relationship based on their common associative mechanisms, with a focus on spatial associations, using analogous tasks and equivalent behavioural measures. The motivation was grounded in the fact that so far, they have primarily been described and compared using different tasks and measures, despite the vast evidence suggesting that WM and LTM are not as different as previously thought. Although not entirely coextensive, one of aspect they have in common is the involvement of the MTL in the effective functioning of their associative mechanisms regardless of timespan (Cabeza et al., 2002; Cohen & Eichenbaum, 1993; Olson et al., 2006). Additionally, it is well established by now that both WM and LTM undergo age-related impairment (Korkki, Richter, Jeyarathnarajah, & Simons, 2020; Lugtmeijer, de Haan, & Kessels, 2019; Peich, Husain, & Bays, 2013; Pertzov, Heider, Liang, & Husain, 2015; Salvato, Patai, & Nobre, 2016). Therefore, to contribute to the uncovering of the complex relationship between the two memory systems, I set out to investigate the associative retrieval abilities of individuals who suffer from degraded WM and LTM, specifically healthy older adults and individuals with pathological memory loss. If the mechanisms guiding the two memory systems are corresponding, then I expected to find similar patterns of impairment, as well as a preserved relationship with age. Conversely, if the two memory systems are supported by sufficiently different mechanisms, they should be differentially affected, and their relationship might erode with time. In this chapter, I will

summarise and review the conclusions of the studies presented and discuss them in the context of existing literature. Additionally, I will address the limitations encountered, emphasise the lessons learned about using different methodologies for testing different populations, and suggest possible avenues for future work.

5.1 Orienting attention internally benefits WM and LTM retrieval in both young and elderly adults

One aspect that has been extensively investigated in WM, but not in LTM, is the positive modulatory effect of top-down attentional mechanism on individuals' retrieval abilities which is preserved in ageing (Griffin & Nobre, 2003; Mok, Myers, Wallis, & Nobre, 2016b; Souza & Oberauer, 2016). Considering that both WM and LTM retrieval suffer age-related impairment, whether there is a process that could effectively ameliorate this decline in certain circumstances is definitely worth exploring. For this reason, the study described in Chapter 2 focused on whether the benefits of retro-cueing extend to LTM processes, and if this could also represent a means to improve LTM memory retrieval performance in elderly individuals. It examined WM and LTM retrieval for the same material - spatial contextual associations - in younger and older adults, and investigated the role that orienting attention internally may play in modulating performance in these two memory systems. Furthermore, as WM and LTM are typically examined separately, using different measures, this chapter also explored whether individuals' abilities to benefit from retro-cues correlate between the two memory systems, and whether this correlation is preserved with ageing. For this, I developed two equivalent retro-cueing memory tasks that incorporated measures of both object identification and object-location binding in WM and LTM. Similar tasks to the ones used have been shown to be sensitive to age-related differences in spatial-contextual associations in previous studies (e.g., Pertzov, Heider, Liang, & Husain, 2015; Salvato, Patai, & Nobre, 2016).

First and foremost, this study confirms the positive modulating effect of retro-cues in LTM (Roüast, 2021), both in young and healthy old adults. The selective retrieval of LTM was

effectively biased by orienting attention internally to relevant targets which improved the quality of LTM memory retrieval by reducing the number of guesses and enhancing localisation precision for both age groups. These results match earlier findings of WM retro-cueing research and extend our knowledge of the effects of internal orienting of attention on retrieval. This is of exceptional significance in ageing, as continuous-report measures have been shown to be more sensitive to age-related changes, reinforcing the reliable effects of this top-down mechanism. Additionally, young individuals were able to benefit more from the use of selective attention to improve their localisation errors. To my knowledge, this is the first study to show that retro-cues are also effective in LTM not only for young, but also for elderly adults. Expanding previous work in the research group (Roüast, 2021), this is also the first study to develop equivalent tasks to measure the effect of orienting attention internally in both WM and LTM, allowing for comparisons and investigations of different patterns of use across the two systems. This was accomplished by adjusting the established retro-cueing approach to measure LTM performance, to look at spatial-contextual associations that are sensitive to ageing deficits.

Consistent with previous research focused on young participants (Griffin & Nobre, 2003; Lepsien, Griffin, Devlin, & Nobre, 2005; Souza & Oberauer, 2016; Souza, Rerko, & Oberauer, 2016), the findings also confirmed that older individuals were also able to use retro-cues to benefit their WM retrieval and, notably, in this case these benefits occurred within complex scenes. Similarly, to previous results from studies of young adults, retro-cues improved participants' access to the target information, but not the quality of memory retrieval. Until this point, studies investigating the effect of retro-cues on old adults' WM retrieval have yielded mixed results (Duarte et al., 2013; Gilchrist, Duarte, & Verhaeghen, 2016; Mok et al., 2016; Newsome et al., 2015). However, this inconsistency could stem from using binary choice tasks that are less sensitive to subtle behavioural differences between cue conditions. Both this current study and the one presented by Mok and colleagues (2016) revealed that retro-cues improve WM retrieval abilities of healthy elderly adults using continuous-report measures (Mok et al., 2016). Furthermore, this is the first study to find a

mediating effect of retro-cues for improved WM retrieval in old adults using complex stimuli, such as real-life everyday objects and scenes, compared, for example, to oriented coloured bars. Importantly, this demonstrates that the benefits of retro-cueing are preserved even when complexity and task demand increase, in contexts more similar to our daily lives.

When comparing the way the two memory systems benefitted from retro-cueing, different patterns emerged. While retro-cues improved access to memories held in WM, the resolution of memory retrieval was improved in LTM. The fact that the two memory systems cued in different brain states may be a possible explanation. While the cues are provided during WM maintenance, information from LTM is outside of the scope of attention, therefore retro-cues mediate retrieval processes. Alternatively, these diverging patterns could stem from differences between the two memory systems: whereas WM maintains limited information that retro-cues aim to filter based on task relevance, LTM, like perception of the external world, offers a broader pool of information to select from.

5.2 WM, LTM and their relationship in healthy ageing and disease

Ageing research is both an important area of interest considering the increase in ageing population as well as a useful tool for uncovering new insights into the mechanisms, patterns of use and interplay between several cognitive functions. Similarly, patient studies have enabled some of the greatest breakthroughs in the field of memory and continue to facilitate closer examinations of the effect of localised injuries on different functions that would be inaccessible otherwise in humans. The changes MTL-based WM, LTM and their relationship undergo in ageing have been the principal focus of this thesis and have been explored in all three empirical chapters.

Consistently, older adults displayed significant impairments in performance across all measures as compared to the young group. This was the case for all four tasks used in the three chapters of this thesis comparing young and old adults, across all testing modalities and memory timespans. Old individuals' decreased memory abilities manifested as slower

response times, lower accuracies in remembering object identities and greater localisation errors when asked to place back target objects in their remembered locations both in two-dimensional and three-dimensional scenes and environments. These findings are in in agreement with several previous studies that showed age-related deficits in both memory systems (e.g., Korkki et al., 2020; Lugtmeijer et al., 2019; Naveh-Benjamin, 2000; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003; Pertzov et al., 2015; Salvato et al., 2016). What is more, all tasks allowed for the investigation of participants' associative abilities. This was achieved through the calculation of mis-binding errors represented by participants' swap rates, meaning how frequently they placed the target object in the encoded location of the non-target. The findings showed that old individuals make more mis-binding errors compared to young adults, reinforcing the associative deficit theory of ageing (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000) and indicating that the age-related decline identified might stem from atrophic changes in the MTL typically observed later in life.

It is important to note that earlier studies showing similar deficits used separate tasks to measure WM and LTM retrieval across ageing that differed in their encoding procedures, stimuli, measures, and memory load. This did not allow for appropriate direct comparisons or examination of their relationship. Unlike these studies, WM and LTM were measured and compared using analogous tasks and equivalent measures in each chapter of this thesis. This enabled their direct comparison, an examination of their relationship and a comparison of the relationships between age groups.

First, exploring the relationship between the way WM and LTM retrieval were modulated by retro-cues and comparing these correlations between age groups revealed differences between the two memory systems. I observed a lack of correlations between the retro-cueing benefits between WM and LTM, particularly in elderly adults, as well as age-related differences in the patterns of retro-cues benefits. The relationship between retro-cueing benefits in WM and benefits in LTM was considerably different between the two groups, younger adults displaying a strong positive correlation which was not observed in old

adults. One possible interpretation could invoke the involvement of brain networks of WM and LTM retrieval that are differentially vulnerable to age-related decline. Besides the contributions of the MTL, the prefrontal cortex is known to play an important role for encoding, maintenance and manipulation of information in WM (D'Esposito et al., 2000). This could explain the differences in the two memory systems, assuming the different rates of impairment of the two structures could lead to an erosion in the strength of correlations in old age. Another source of variance is the separate encoding task participants were given prior to LTM retrieval. The strength of encoding likely differed between the two age groups, as indicated by their learning results. Additionally, orienting attention internally for selective retrieval may differ structurally or functionally between WM and LTM, considering that this is achieved in separate brain states. For this reason, an individual's use of retro-cues in WM may not rely on the same mechanisms as their benefits in LTM.

Comparing the two memory systems' decline in ageing in Chapter 3 revealed that, despite both groups' improvement from WM to LTM measured after a 20-minute delay, neither young nor old participants improve further on the second day of testing. In fact, old adults displayed considerable forgetting or decrement in performance, unlike the younger group. This could indicate a subtle deficit in memory consolidation. Similar findings were presented by Huppert and Kopelman (1989) when comparing young and old healthy adults' retrieval performance on a visuospatial task after ten minutes, 24 hours and 1-week post-encoding delay. They revealed significant differences in forgetting rates within the first 24 hours. The cause of pronounced forgetting could stem either from deficient encoding abilities in old participants, decreased retrieval abilities or a mix of both. To tease apart the cause, I included the number of times each object was encoded as a covariate in the analyses, but the results remained unchanged. Future studies should introduce changes in the task design that would allow for a better understanding of the source of these differences. For example, training participants to an established criterion before measuring their long-term retrieval abilities could be a solution.

Examining the relationship between the two memory systems using the navigation-based tasks in Chapter 3 revealed that young participants' performance after a 20-minute delay correlated both with their WM and their performance on the next consecutive day. This was not the case for old individuals who did not yield any significant correlations. As discussed throughout the thesis, memories for object-location associations are thought to rely on the MTL regardless of memory timespan (e.g., Kolarik, Baer, Shahlaie, Yonelinas, & Ekstrom, 2018; Zokaei et al., 2019). However, WM is also known to rely on the prefrontal cortex for encoding, maintenance and manipulation of the information (D'Esposito et al., 2000). The different rate of impairment of the two structures and their functional connections could lead to an erosion in the strength of correlations in old age. Additionally, the relationships between WM and LTM measured after 20 minutes were not found to differ between groups, indicating the pattern of use for shorter periods of time remains consistent with ageing. However, the relationship within LTM tested at different timepoints seemed to change with time, strengthening the finding that elderly participants have increased forgetting tendencies. It is important to note that old individuals' pronounced forgetting is unlikely caused by associative deficiencies, as the rate of their mis-binding errors remained consistent from the first to the second day of testing. Future studies should further explore these divergent patters, as they could also become markers of unhealthy ageing.

Overall, these studies of healthy ageing emphasise important similarities and differences between WM and LTM using equivalent measures. First, I learned that the two memory systems might rely on different mechanisms of orienting selective attention internally. Testing this hypothesis using different imaging methods could reveal the extent of the overlap. Next, these findings suggest that, in line with existing literature, both memory systems undergo age-related associative decline, reemphasising the shared contribution of the MTL. Lastly, these studies revealed that the relationship between the two memory systems is preserved in ageing adults, but that this erodes within LTM after 24 hours after encoding.

To expand the understanding of the MTL-based WM and LTM retrieval, Chapter 4 focused on the retrieval abilities of a clinical cohort of individuals with LE with localised MTL damage. They were asked to perform the same navigation-based task measuring both WM and LTM, and their abilities were compared to those of healthy old adults. Previous studies with individuals with LE found that WM retrieval impairment was observed when maintaining multiple items and that this was not caused by poor memory of individual object features, but instead by an inability to bind different features together, an MTL-dependant ability (Pertzov et al., 2013). LTM impairment in individuals with LE has also been found in several studies using a broad range of tests. Most recently, Argyropoulos et al. (2019) characterised the same LE cohort and specified that they showed pronounced episodic memory retrieval impairment of both verbal and visual material, demonstrating prominent forgetting of visual material (Argyropoulos et al., 2019). However, the study in Chapter 4 showed the opposite. When comparing the two groups' performance in WM and LTM, the results showed that overall they did not differ in their errors when retrieving target locations. Most likely, the lack of a significant interaction between group and memory type, in this case, is the result of the small sample size which only allowed for underpowered statistical tests. Alternatively, an earlier study previously showed that while retrieving locations relative to environmental boundaries relies on the hippocampus, remembering locations relative to environmental landmarks depends on the caudate nucleus (Doeller & Burgess, 2008). Generalising to the current study, where environmental boundaries were not clearly delimited in all environments, which instead provided numerous landmarks, the seemingly unimpaired performance of individuals with LE could imply that they might have been able to retrieve objects' locations relative to local landmarks, due to their spared caudate (Argyropoulos et al., 2019). This is also a cue for future studies to consider a distinction in their environments' design that could separate boundary-based from landmark-based navigation. Although the results of Chapter 4 remain inconclusive because of the small number of participants and low statistical power and, this study provides a good bases for future work with the same goal. The fact that individuals with

LE could tolerate and complete the task is a good starting point which could lead to significant results in the appropriate circumstances.

5.3 Implications and future work

This thesis introduced two novel tasks that enable quantifying spatial associative abilities in analogous ways for WM and LTM, producing interesting results that complement existing literature, open new avenues for future research and provide the necessary tools to continue exploring the two memory systems in equivalent, comparable ways. Some of these implications and possible trajectories of future work are presented below.

Building on earlier work from the research lab (Roüast, 2021), the study in Chapter 2 was, to my knowledge, the first to investigate and compare the effects of retro-cueing on memories of different timescales in two age groups using equivalent sensitive continuous report measures. In the retrieval phase of each task, spatial informative retro-cues indicated the left or right half of the scene where the target object was previously located before a choice between two objects was made to indicate which had been present in the scene. This decision was relatively simple and ceiling accuracy performance was observed, particularly in young adults, across conditions. Future studies could introduce some changes to the task design to increase the difficulty of this perceptual requirement and emphasise this measure. For example, this could consist of providing a choice between items from the same category or varying the retro-cue reliability resulting in a wider distribution of the accuracy variable.

Another notable aspect pertaining to the design of the retro-cueing tasks that future studies should consider is the nature of the retro-cue. Continuing to explore the effect of orienting attention in LTM, follow-up research should test whether similar effects are identified when using, for example, verbal cues. These were proven effective by Lepsien and colleagues who used letters to suggest which category of items (faces or scenes) was to be retrieved (Lepsien et al., 2011). These comparisons are particularly relevant for studies involving older adults, as it is well established that semantic memory is typically spared by

healthy ageing (e.g., Kausler, 1994). As such, old adults may benefit from these intact functions and capitalise on the benefits of retro-cues to a greater extent. Additionally, studies should compare whether the effectiveness of different types of retro-cues is modulated by memory timespan.

In the same realm lays the question of whether the benefit provided by retro-cues is limited to the retrieval of the cued feature. If that is the case, spatial retro-cues would only enhance the retrieval of items' locations, whereas colour-related cues would be limited to improving colour retrieval. Alternatively, are retro-cues able to facilitate access to more complex multi-featured memories? This is questions is of particular relevance for studies focused on the benefit of retro-cues in LTM, given that whereas WM maintains a limited amount of information filtered based on task relevance, LTM, like perception of the external world, provides a much larger pool of complex stimuli to select from.

To reveal whether WM and LTM are differentially modulated by attention, future studies should also consider certain theories aiming to describe the mechanism of WM retro-cueing which suggested an impairment in the memory for non-cued items and memory costs for invalid-cued items (Souza & Oberauer, 2016). Would this also be the case in LTM? The current tasks could also provide a basis for future experiments, that may also use invalid cues to determine their effect and tease apart different mechanisms of use. An additional free recall task could also be used to assess and compare participants' memory for differently cued items.

The study in Chapter 2 and the proposed retro-cueing tasks to measured benefits on associative WM and LTM in equivalent ways represents a great starting point for exploring and comparing the effects of orienting attention within the two memory systems. As discussed in the chapter, this experimental approach can be used to incorporate different avenues of research and several methodologies, such as EEG, eye-tracking, or fMRI. This adaptability makes the tasks appropriate for numerous behavioural and neural enquiries. The engaging nature of the tasks and their reduced difficulty levels also make it suitable for different kinds of studies and populations, such as children or clinical cohorts. However, one disadvantage of

the tasks proposed is the possibility that participants may have been affected by centre bias, leading to distorted responses located closer to the centre of the screen. Several earlier studies of selective attention in scenes found that participants' focus was drawn to the centre of static images (Foulsham & Underwood, 2008; Parkhurst, Law, & Niebur, 2002; Tatler, Baddeley, & Gilchrist, 2005). This becomes problematic for most spatial recall tasks using two-dimensional scenes. Therefore, one solution could be using three-dimensional virtual environments which could enhance ecological validity, particularly when they increase the level of immersion.

The efficacy of these immersive methods of measuring memory for object-location associations in both young and old adults was explored in Chapter 3. Increasing in complexity to resemble real life demands, the first study presented in this chapter compared the performance of young and old healthy adults in a navigation-based memory task on two devices – a personal computer and an immersive VR device –to determine whether old individuals benefit from an increased level of immersion. Despite the numerous experimental limitations encountered during implementation, leading to early termination, the study's most important takeaway message consisted of suggestions for how future research could address these challenges and improve testing of older adults using appropriate VR technologies and improved task designs. Some of the difficulties of this experiment stem from participants' lack of understanding of the technology involved in performing the tasks. In the future, this difficulty might be alleviated as digital devices become increasingly integrated in everyday life. Meanwhile, future studies could consider measures to ensure that data collected from older adults are not confounded by their limited understanding of and suboptimal interaction with the devices. One solution could be providing sufficient training for participants to become familiar to using the hardware necessary. This way, not having to focus on the correct use of technology may free up cognitive resources required to perform and engage with the task to the best of their abilities. Although this study did not shed light on the best means to measure these functions, it provided important lessons for designing future tasks that informed the second study presented in Chapter 3.

To my knowledge, this was the first human study to compare navigation-based spatial associative WM and LTM memories in two age groups and to test their relationship, using equivalent sensitive continuous report measures within the same task. The findings suggest that the relationship between WM and LTM is preserved in healthy ageing, reemphasising the possible overlap of their underlying mechanisms that decline with age. However, what supports this relationship is not entirely clear. Information was encoded identically, and retrieval abilities were probed in analogous way, although the delays before encoding and retrieval differed. Variability in performance between the two groups may stem from different effects of ageing at any of these stages. Ageing affects the structure and function of the MTL, known to support associative processes in both memory systems (Gorbach et al., 2017; Henson et al., 2016; Trelle et al., 2020), as well as other structures such as the occipital cortex, thought to contribute to the quality of granular representations in both WM and LTM (Chamberlain et al., 2021; Pitchaimuthu et al., 2017). For this reason, these structures become a likely source of variability in WM and LTM and future studies should combine additional imaging methods to examine how the integrity of these areas relates to performance in WM and LTM, using equivalent comparable tasks such as the one designed and presented in Chapter 3. Together, these results may reveal the extent to which differential ageing of the brain contributes to distinct patterns of memory impairment.

Lastly, variability between the two memory systems and their relationship could also arise from the extent of atrophy of the supporting mechanisms at an individual level. For example, a longitudinal study found that age-related reductions in brain volumes on average affected the frontoparietal network know to play a key role in WM and the MTL supporting both associative processes and LTM retrieval, in comparable ways, but revealed significant individual differences (Maillet & Rajah, 2014; Raz et al., 2005; Rottschy et al., 2012). This may also be an underlying reason of the lack of correlations in old individual's performance in WM and LTM.

5.4 Limitations

All studies presented in this thesis suffered from several limitations. Although some of these proved impactful enough to impede the generalisability of some of the findings, they should be regarded as important lessons that aim to equally inform future research.

A prominent drawback encountered across all studies presented was the number of trials for each condition tested within each task. Generally, future studies should ensure a large enough number of trials to not compromise statistical power and to allow for additional statistical analyses that were not accessible in this case. For example, the small number of trials was a limiting factor for the three-parameter two-dimensional mixture model fitted to the localisation error data in Chapter 2 to tease out the sources of participants' errors, as previous studies have showed that the higher number of trials the better the accuracy and fit of the model (e.g., Grogan et al., 2020). Increasing the number of trials in the second study of Chapter 3 and Chapter 4 would also allow for a clear separation of the effects of ageing on spatial memory from encoding deficits, by training both age groups to a set criterion prior to probing their retrieval abilities.

Low sample sizes also restricted the statistical analyses available to interpret the data and the generalisability of the findings. This was the case for the first study presented in Chapter 3 and the study in Chapter 4, focused on participants with LE. This was an unfortunate consequence of the ongoing COVID-19 pandemic. The project involved behavioural testing of healthy elderly controls and elderly participants with LE, all over 60 years old, achieved either in Oxford, which required them to travel, or at their homes which involved me visiting, also increasing their risk of infection. Testing had to be cancelled and could not resume before the completion of the thesis. For this reason, the studies were adapted and, in the interest of completeness, both descriptive and statistical results were presented. However, future studies should focus on collecting a complete dataset to reveal interesting new findings that are not statistically underpowered.

In terms of task design, the studies using virtual three-dimensional environments emphasised several aspects that should be considered to ensure the appropriate collection of complex datasets. First, in the study comparing participants' performance on a PC and in an immersive VR environment, the environment remained identical between the two devices. This may have introduced a source of interference between the two versions of the task. It is possible that, on the second testing device, associations from the first testing device caused proactive interference. Therefore, participants may have retrieved locations corresponding to objects encoded in the first version they performed. A solution to prevent this type of interference could be introducing changes and variations of features in the virtual environment, like in the task developed for the second study of Chapter 3. However, that task provided its own design limitations. Specifically, the different layouts of the environments used and the fact that the obstacles were not impenetrable did not allow the use of path efficiency as a measure of performance.

Using the appropriate technology was also an important lesson learned in trying to find the optimal method to probe old adults' spatial memory retrieval. The hardware used to create the immersive VR experience had several limitations which may have compromised the immersive experience. When worn by a participant, the VR headset left two gaps on either side, which could disrupt the immersive experience, as they acted as avenues for additional light and confounding visual stimuli. Although they were covered using opaque duct tape which blocked the light, the gaps were not always entirely covered to not to stick to participants' skin, and several participants mentioned that they were aware of their location in the testing room. Not only this was disrupting the immersive experience, but it probably also increased the likelihood of cybersickness causing disorientation. What is more, to achieve stereoscopic vision, participants were asked to adjust the lenses of the headset themselves to fit their physiognomy. The researcher could not to verify that 3D vision was achieved and that participants did not rely on blurry or distorted visual input that could impact performance. These limitations did not only prevent the generalisability of the results, but also drastically

reduced the number of participants by becoming a cause of cybersickness, further reducing the statistical power and reliability of the findings.

Fatigue is another factor that should be considered, particularly when testing old adults and individuals from a clinical cohort who have reduced resources. Mental fatigue has been shown to significantly impact everyday task performance, reducing concentration and increasing distractibility (Boksem, Meijman, & Lorist, 2005). This likely affected participants' performance. Particularly, participants with LE performed the task presented in Chapter 4 within a session which included two additional experiments and a set of several questionnaires.

5.5 Conclusion

To conclude, this thesis compared spatial associative WM and LTM performance in healthy ageing and in the presence of MTL impairment. The studies presented explored the mechanisms and interplay of the two memory systems, as well as the modulatory relationship between them and top-down attentional processes, using analogous tasks and equivalent behavioural measures. The findings propose that both memory systems undergo similar age-related associative decline, reemphasising the shared contribution of the MTL and that the relationship between the two memory systems is preserved in ageing, despite old adults' increased forgetting within 24 hours after encoding. This implies possible similarities in the underlying neural mechanisms of the two memory systems, although further investigation is required to validate this assumption and determine the extent of the overlap. Lastly, this thesis also found that WM and LTM may rely on different mechanisms of orienting selective attention internally. Small sample sizes of the LE cohort did not allow for pertinent interpretations of the results. However, the most significant outcomes of this thesis remain the two tasks developed to measure spatial associative memory of different timespans in equivalent ways, and to investigate and compare the effects of retro-cues on the retrieval of the two memory systems using analogous steps and stimuli. Taken further and complemented

by neuroimaging methods, these can become great tools in the research of WM and LTM retrieval processes and in development of sensitive measures equally suitable for ageing and clinical studies.

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